DOES NOT CIRCULATE

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, PP. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1954

ORIGINAL ARTICLES

OBSERVATIONS ON A SELECTED ANTIBIOTIC COMBINATION*

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The temptation to use a combination of antibiotics in the treatment of infections is a practical, everyday problem. It arises primarily from the fact that no single antibiotic is currently available with a sufficiently broad antimicrobial spectrum to be effective in mixed infections that will so interfere with the adaptive processes of microörganisms so as to preclude the development of resistance and that does not induce untoward reactions under conditions of adequate dosage. Furthermore, clinical experience has demonstrated that better therapeutic results have been obtained in certain infections with some combinations of agents than with single drugs alone. It is, therefore, not difficult to understand the problem which confronts a practicing physician who has at his disposal a number of clinically useful agents, each of which alone is incapable of producing the desired effect in a given case. What reliable information is available which will assist him in selecting the antibiotics to be used in combination under appropriate indications?

With this in view, there have been made within recent years, numerous studies dealing with antibiotic combinations. For the most part, the major effort in this field of chemotherapeutic research has been confined to *in vitro* observations on a limited number of antibiotic combinations and bacteria. A few studies have been concerned with attempts to apply these findings to experimental animals and only a very few deal with therapeutic trials in humans.

Aside from the antibiotic synergism occurring with penicillin and streptomycin against the enterococcus, streptomycin and the broad spectrum agents against Brucella, and bacitracin and penicillin against staphylococcus, there is considerable diversity of opinion re-

*Presented in part before the Sixty-sixth Meeting of the American Clinical and Climatological Association, Hot Springs, Virginia, November 3, 1953.

garding the use and status of other antibiotic combinations in clinical medicine. Recently Jawetz and his associates[13] published a scheme, based primarily on their own *in vitro* and animal studies and secondarily on their interpretation of reports by others, which was suggested as a guide in predicting the usefulness of antibiotic combinations. This scheme is based on observation of a change in rate of bactericidal action observed when certain antibiotics are added to others. Increased rate of bactericidal action is defined as synergism, while a diminution of the same effect is defined as antagonism. The clinically useful antibiotics are divided into two groups: Group I comprises penicillin, streptomycin, bacitracin, and neomycin. These are often synergistic with each other, occasionally indifferent, and never antagonistic. Group II comprises chlortetracycline, oxytetracycline, and chloramphenicol which are neither synergistic or antagonistic to each other, and very often are additive. Antibiotics in this group frequently antagonize the activity of agents in Group I when the latter are acting on susceptible organisms.

In our opinion, it is indeed regrettable that the postulation of this scheme by Jawetz and his associates[13] should have resulted in connotations which were, quite possibly, never intended by the authors. At first, Jawetz and his associates, by *in vitro* experiments, demonstrated that the bactericidal rate of penicillin was retarded by the addition of either chloramphenicol[14], chlortetracycline, or oxytetracycline[11]. The observed interference was characterized as being unilateral, occurring maximally when the bactericidal activity of the penicillin was greatest and when the concentration of the antagonizing agent was bacteriostatic and yet the combination was capable of a progressive bactericidal action which ultimately sterilized the culture. Significantly, the interference phenomenon could not be demonstrated with all strains of enterococci, group A streptococci, and Friedlander bacilli studied. Later, *in vivo* experiments, utilizing mice infected with group A streptococci, revealed a higher mortality rate in animals receiving both penicillin subcutaneously and chloramphenicol intraperitoneally than in those receiving penicillin alone. A similar finding could be demonstrated only with difficulty in mice infected with *K. pneumoniae* and treated with multiple doses of penicillin, with chlortetracycline or oxytetracycline as the antagonizing drugs. Other workers[1,3,16] have been unable to confirm the Jawetz observations and, in some instances, even reported a synergistic effect with the same combinations reported by Jawetz as being antagonistic. While such conflicting findings may well be explicable on the basis of differences in bacterial strain, technical procedure, and definition of synergism and antagonism, they forcibly emphasize our current lack of knowledge of the activities of antibiotic combinations.

For the past 3 years, we have been engaged in a comprehensive, but by no means exhaustive, investigation of antibiotic combinations. Our objectives were three-fold: (a) to evaluate systematically, by suitable *in vitro* procedures, the clinically useful antibiotics separately and in combination, from the standpoint of ability to inhibit growth of a few arbitrarily selected Gram-positive and Gram-negative organisms. This preliminary screening was intended to reveal unusual combinations. (b) To screen the unusual combination, or combinations, more intensively against large numbers of generically dissimilar bacteria routinely isolated from clinical specimens. (c) Any combination, or combinations, revealed by this more

intensive screening operation to be tested in the clinic for *in vivo* efficacy.

The present report is concerned with findings relative to these objectives.

DEFINITIONS. In a previous publication[4], one of us has stated that laboratory studies of antibiotic combinations should include: (a) A determination of the lowest concentration of each agent, which, under specified conditions, interferes with one or more functions essential to normal bacterial reproduction to the point where there is no detectable growth macroscopically. This concentration is commonly called the minimum inhibiting concentration (M. I. C.) and is most frequently and conveniently determined by a serial dilution procedure. This type of test indicates only that growth inhibition has occurred, but does not differentiate as to whether the inhibition is temporary (bacteriostatic) or permanent (bactericidal). (b) Determinations to establish the relative permanency of the observed inhibition and to be made in appropriate sequence on the same bacterial population. This information is most readily obtainable by the application of plating procedures, and will be most meaningful if the entire contents of all tubes which show no macroscopic growth are tested. (c) Simultaneous testing of antibiotic combinations by identical procedures.

The rationale for the above recommendations is obvious when it is considered that the antibacterial effects of all antibiotics are manifested either as temporary or permanent growth inhibition and that a knowledge of both manifestations is more desirable than a knowledge of only one or the other. Thus, the application of both of these procedures to a single population of bacteria will yield data regarding the concentration of agent, separately as well as in mixtures in which it is present, required to produce both bacteriostatic and bactericidal effects.

It should be remembered that the term bacteriostasis should apply only to those situations in which there is no change in the number of viable bacteria during the time of exposure to an inhibitory compound. That it is frequently impossible to satisfy this criterion is readily appreciated, when it is realized that when the reproductive and/or growth processes of an organism are retarded, such an organism may readily die of starvation and senescence. Thus, after an appropriate lapse of time there may be a gradual, but significant, decrease in total numbers. Therefore, it would seem that the sole valid distinction between bacteriostatic and bactericidal effects rests on the rate at which bacterial numbers decline; the rate being greater with bactericidal than with bacteriostatic agents.

The terms synergism, antagonism, additive and indifferent have been used by others to describe the effect of the addition of one or more antibiotics on the activity of another. In this paper, the term synergism will be applied to those antibiotic combinations producing a given effect (bacteriostatic, bactericidal, or both) and in which the concentration of each component contributing to this effect is less than that required to produce the same effect when the component acts individually; the magnitude of the difference being at least four-fold. Thus, combinations will be designated as showing synergism rather than its constituents synergizing each other's activity. For example, if in the combination of chlortetracycline, oxytetracycline, and chloramphenicol a concentration of 0.3 mcg. per cc. of each is required for bacteriostatic effect, and, at the same time, concentrations of 1.25, 2.5, and 1.25 mcg. per cc. respectively are required to

produce the same effect when they are used singly, then the combination shows synergism according to our definition above. The definition of antagonism is made on a similar basis, except, of course, that the concentration is increased to the same degree. According to these definitions, it is possible for a combination to be synergistic with respect to bacteriostasis only, to bactericidal effect only, or to both.

MATERIALS AND METHODS. Details regarding composition and preparation of culture media, antibiotic solutions, test inocula and procedures have been described elsewhere[8,9]. All organisms used were isolated from clinical specimens submitted to the laboratory for routine bacteriological examination.

Results and Discussion. Preliminary screening tests employing the various antibiotics (penicillin, streptomycin, chlortetracycline, oxytetracycline, and chloramphenicol) separately and in 26 different combinations against strains of *Micrococcus pyogenes var. aureus* and *K. pneumoniae* Type A, indicated that combinations of chlortetracycline, oxytetracycline, and penicillin and chlortetracycline, oxytetracycline, and chloramphenicol showed both bacteriostatic and bactericidal synergism against these organisms, respectively. Further evaluation of these two combinations against individual composite cultures of *Micrococcus pyogenes var. aureus, Streptococci (viridans, pyogenes, enterococcus), Coliforms, S. typhosa, K. pneumoniae* Types A and B, *Ps. aeruginosa*, and *Proteus sp.*, totaling 258 individual strains, indicated that the combination of chlortetracycline, oxytetracycline, and chloramphenicol was superior to the chlortetracycline, oxytetracycline, and penicillin combinations[8]. Illustrative results, as indicated in Table 1, show the superiority of the combination COC over its individual components.

TABLE 1.—COMPARATIVE ACTIVITY OF COC VS. INDIVIDUAL COMPONENTS AGAINST COMPOSITE INOCULA OF REPRESENTATIVE BACTERIAL PATHOGENS

		Concentration Required for Inhibition (mcg./cc.)							
	Number of	*C**		*O***		*C****		*COC*	
Organism	*Strains*	*I*†	*II*‡	*I*	*II*	*I*	*II*	*I*	*II*
M. pyogenes var. aureus	50	80.	80. +	80. +	80. +	80.	80. +	2.5	20.
Enterococcus	19	2.5	80. +	2.5	80.	10.	80. +	0.15	20.
Coli-aerogenes	44	5.	80. +	5.	80. +	40.	80. +	0.6	40.
K. pneumoniae	18	2.5	80. +	2.5	80. +	10.	80. +	0.6	20.
S. typhosa	27	1.25	80. +	1.25	80. +	2.5	80. +	0.3	20.
Proteus sp.	13	80. +	80. +	80. +	80. +	40.	80. +	5.	40.

* Chlortetracycline
** Oxytetracycline
*** Chloramphenicol

† Bacteriostatic Inhibition
‡ Bactericidal (100%) Inhibition

As additional corroboration for the above findings, a survey of the antibiotic susceptibilities of 2173 individual bacteria was carried out, in order to compare the incidence of susceptibility to chlortetracycline, oxytetracycline, chloramphenicol combination with that of its individual constituents. The criterion for distinguishing between susceptible and resistant organisms is the observation of the presence or absence of a zone of inhibition, regardless of diameter, surrounding filter paper discs containing a specified amount of antibiotic[10]. This amount corresponds to

the average maximum serum concentration attainable in average patients receiving the most commonly prescribed dosages. Data on penicillin and streptomycin have been included because of the frequency with which these agents are considered for use against Gram-positive and Gram-negative organisms, respectively. The dosages, serum antibiotic concentration, and criterion for interpretation of susceptibility, are summarized in Table 2.

Shown in Table 3 is the percentage of organisms classified as susceptible

TABLE 2.—CRITERIA FOR DETERMINATION OF RELATIVE SUSCEPTIBILITY

Antibiotic	*Dosage*	*Blood Concentration*	*Disc Antibiotic Concentration*	*Inhibition Zone*	
				Present	*Absent*
Penicillin (cryst.)	100,000 q. 3 h	0.75–1.0 u/cc.	1.0 u	S*	R**
Penicillin (procaine)	300,000 o.d.				
Streptomycin	0.5 gm. B.I.D.	15 mcg./cc.	15 mcg.	S	R
Chlortetracycline	0.5 gm. q. 6 h	4 mcg./cc.	4 mcg.	S	R
Oxytetracycline	0.5 gm. q. 6 h	6 mcg./cc.	6 mcg.	S	R
Chloramphenicol	0.5 gm. q. 6 h	15 mcg./cc.	15 mcg.	S	R
COC	0.5 gm. q. 6 h†	See below‡	C—1.25 mcg.‡ O—2.0 mcg. C—5.0 mcg.	S	R

* S = Susceptible
** R = Resistant

† 0.5 gm. represents total amount of combination consisting of equal parts by weight of chlortetracycline HCl, oxytetracycline HCl, and chloramphenicol.

‡ Up to the present time, we have been unable to find in the literature or to devise a quantitative procedure for the determination of either the total serum antibiotic concentration or its composition following administration of the combination. Lacking evidence to the contrary, we have assumed that absorption of any one of the constituents into the blood is independent of that of the others and proportional within limits to the dose. Since the dose of the separate agents comprising the combination is ⅓ of that when they are used separately, the expected serum concentrations would be expected to be proportionally diminished. For this reason, the COC disc was prepared to contain 1.25 mcg. chlortetracycline, 2.0 mcg. oxytetracycline, and 5.0 mcg. chloramphenicol.

TABLE 3.—RELATIVE ANTIBIOTIC SUSCEPTIBILITY OF BACTERIA ISOLATED FROM ROUTINE CLINICAL SPECIMENS*

Organism	*Total Strains*	*Per Cent Susceptible to*					
		P	*S*	*C***	*O*	*C*†	*COC*
Str. viridans	107	99.1	—	100.	100.	100.	100.
Str. pyogenes	38	100.	—	100.	100.	100.	100.
D. pneumoniae	105	100.	—	100.	100.	100.	100.
M. p. var. aureus	475	29.9	—	85.0	81.8	87.5	95.6
Alpha enterococcus	283	33.2	—	82.8	78.4	82.8	93.3
Beta enterococcus	85	28.2	—	57.7	55.3	79.8	84.8
Total	1093	46.5	—	86.0	82.8	88.5	95.0
H. influenzae	47	—	93.6	100.	100.	100.	100.
Coli-aerogenes	447	—	61.0	33.4	48.7	83.3	94.3
Klebsiella Sp.	139	—	43.2	40.2	51.7	65.4	92.0
Paracolon Sp.	109	—	49.6	20.2	29.4	64.1	61.5
Proteus Sp.	224	—	23.2	3.1	7.9	32.1	33.9
Ps. aeruginosa	114	—	9.7	4.4	18.4	6.1	11.4
Total	1080	—	45.7	26.5	37.7	60.8	69.7
Grand Total	2173	—	—	56.4	60.6	74.8	82.7

* Urine, sputum, blood, C. S. F., exudates
** Chlortetracycline
† Chloramphenicol

to penicillin, streptomycin, chlortetracycline, oxytetracycline, chloramphenicol, and to the combination, COC. For a clearer presentation, it is desirable to discuss the Gram-positive and Gram-negative bacteria separately.

A. GRAM-POSITIVE BACTERIA. *The* strains of *Streptococcus viridans, Streptococcus pyogenes* and *D. pneumoniae* are uniformly susceptible to the individual antibiotics and to the COC combination. With regard to strains of *Micrococcus pyogenes var. aureus* and the enterococci, it is evident that, while only about 30% are penicillin-susceptible, a significantly greater percentage are sensitive to the broad spectrum antibiotics, and particularly to COC.

Considering the total number (1093) of Gram-positive bacteria studied, it is seen that 95% were susceptible to COC, as compared with 88.5%, 86.0%, and 82.8% for chloramphenicol, chlortetracycline, or oxytetracycline, respectively. The difference between COC and the other agents is significant, while the difference between the individual broad spectrum agents is not. Considering the 843 strains showing a high incidence of penicillin resistance, 94% were found to be sensitive to COC, 85% to chloramphenicol and about 80% to either chlortetracycline or oxytetracycline. These differences are significant.

TABLE 4.—INCIDENCE OF SUSCEPTIBILITY OF ENTEROCOCCI (74 STRAINS) TO CONCENTRATIONS OF THE INDIVIDUAL AGENTS COMBINED IN COC

Agent	*Concentration (mcg./cc.)*	*Incidence of Susceptibility (%)*
Chlortetracycline	1.25	28.3
Oxytetracycline	2.	29.7
Chloramphenicol	5.	18.9
COC, containing C, O, C combined in same amounts		77.0

While the differences in the percentage of strains of Alpha hemolytic enterococci and *Micrococcus pyogenes var. aureus* susceptible to chlortetracycline, oxytetracycline, or chloramphenicol are not statistically significant, the difference between these agents and the COC combination is. While no significant difference can be demonstrated between the percentage of strains of Beta enterococci susceptible to chloramphenicol and to COC, these agents are significantly superior to either chlortetracycline or oxytetracycline, whose activity is approximately the same. It is shown above (Table 4) that the apparently equal activity of COC against these organisms is not due to the activity of any single one of its components.

B. GRAM-NEGATIVE BACTERIA. The strains of *H. influenzae* are uniformly susceptible to the individual antibiotics and to COC, while for all practical purposes *Ps. aeruginosa* may be considered as resistant to the same agents. With organisms of the Coli-aerogenes and Klebsiella groups, incidence of susceptibility to COC was greater than that to either streptomycin, chloramphenicol, chlortetracycline, or oxytetracycline. In the case of *Paracolon* and *Proteus* species, incidence of susceptibility to COC was about the same as to chloramphenicol (60%), but significantly higher than to either streptomycin, chlortetracycline, or oxytetracycline. However, the majority of strains (65%) of *Proteus* were resistant even to COC. Studies now in progress

indicate that antibiotic susceptibility of *Proteus* strains is related to species differences; the *vulgaris* and *morgani* being significantly more susceptible than *mirabilis* and *rettgeri* species.

Of the 1080 Gram-negative bacteria studied, about 70% were susceptible to COC, 61% to chloramphenicol, 46% to streptomycin, 38% to oxytetracycline, and 27% to chlortetracycline. The apparent ineffectiveness of chlortetracycline may be attributable to the recognized instability of this agent under *in vitro* conditions, although, if the incidence of susceptible strains is a measure of this stability, it is not reflected to the same degree against Gram-positive organisms.

incidence of susceptibility of Alpha hemolytic enterococci to concentrations of chlortetracycline, oxytetracycline, or chloramphenicol corresponding to those in which these agents are combined in COC.

While this work was in progress, reports on two new antibiotics, erythromycin[12,15] and carbomycin[17], indicated that these agents appeared to be particularly effective against penicillin-resistant staphylococci and enterococci. It seemed of interest to compare the incidence of susceptibility of these organisms to the newer agents and COC[7]. Data relative to this comparison are shown in Table 5. In the case of *Micrococcus pyogenes var. albus* and

TABLE 5. TOTAL NUMBER AND INCIDENCE OF SUSCEPTIBILITY (%) OF COCCI TO THE DIFFERENT AGENTS

	M. pyogenes var.		*Enterococcus*		
	aureus	*albus*	*alpha*	*beta*	*Total*
No. of Strains	255	135	150	52	592
Per cent Susceptible to:					
Penicillin	27.4	56.2	57.3	40.4	41.6
Oxytetracycline	73.7	77.9	82.0	59.6	75.6
Chlortetracycline	72.5	78.6	87.3	63.5	76.8
COC	92.5	92.6	92.9	90.5	93.5
Carbomycin	98.8	94.0	90.6	90.5	95.0
Erythromycin	99.2	99.2	99.4	94.3	98.8

Of the 2173 strains included in this study, about 83% were susceptible to COC, as compared with 75%, 56%, and 61% to chloramphenicol, chlortetracycline, or oxytetracycline respectively. Despite the fact that the quantity of chloramphenicol, chlortetracycline, and oxytetracycline in the COC combination was only one-third that when these antibiotics were used alone, it will be noted that the incidence of susceptibility to COC is significantly greater than that to the individual antibiotics.

Additional evidence indicating that the increased incidence of susceptibility to COC is not attributable to any one of its component agents, is presented in Table 4. Here is shown the

Beta hemolytic enterococci, there is no significant difference in percentage of strains susceptible to erythromycin, carbomycin and the COC combination. As regards *Micrococcus pyogenes var. aureus* and Alpha hemolytic enterococci, there is a slightly higher incidence of susceptibility to erythromycin than to either carbomycin or COC, the difference being significant. Of the approximately 600 strains studied, better than 90% were found to be susceptible to all of the agents, although the incidence of susceptibility to erythromycin is slightly but significantly higher than that to carbomycin or to COC (85%).

Clinical Observations. BACTERIAL PNEUMONIA. During the winter of 1952 to 1953, a program was developed at the Philadelphia General Hospital to test the efficacy of several antibiotic regimens in the treatment of bacterial pneumonia. Within the period of this study, 283 patients were admitted to the Medical Wards with a diagnosis of pneumonia[19]. Of these, 95 fulfilled the criteria for the diagnosis of pneumococcal pneumonia: namely, a clinical picture compatible with a diagnosis of primary pneumonia, the isolation of pneumococci from sputum or blood, and/or repeated roentgenographic examinations sufficient in number to establish the fact that the pulmonary lesion was reversible to the point of complete, or almost complete, disappearance over a period of weeks. The remaining 188 cases were discarded for various reasons, the most common being pulmonary tuberculosis in 43, and Klebsiella pneumonia in 24 patients. In this latter group, it must be emphasized that the diagnosis of Klebsiella pneumonia was made largely on the finding of Klebsiella organisms in the sputum, which, in itself, does not establish the fact that the associated pulmonary infection was caused by this bacterium[18].

Of the 95 cases of pneumococcal pneumonia, 38 received procaine penicillin, 300,000 units intramuscularly every 12 hours and 24 were treated with COC, 0.5 gm. every 6 hours by mouth (the remaining cases in this subgroup were treated with erythromycin or carbomycin). The length of treatment varied from 4 to 27 days (10.4 average) in the penicillin-treated group and 4 to 26 days (10 average) in the COC-treated group. The two groups of patients were comparable in various respects. The therapeutic effectiveness was evaluated by the rapidity of the temperature response, the rate of resolution of the pulmonary lesion, the failure to respond after 72 hours of treatment, the development of pulmonary complications, and the mortality rate. On the basis of this evaluation, the results in the two groups of patients were equivalent and satisfactory. In one of the penicillin-treated patients, who failed to respond satisfactorily, the administration of COC was followed by prompt improvement. No severe toxic reactions were noted in either group, but one patient treated with COC developed a stomatitis which was attributed to the drug therapy.

Whereas the pneumococcal pneumonia group of 62 cases was treated with two therapeutic regimens, the 24 Klebsiella cases received 16 different regimens of therapy, ranging from treatment with a single drug to as many as 4 different drugs in succession, including various combinations of drugs. Therefore, it is not possible to make any unequivocal statements regarding the efficacy of any single regimen. However, it is noteworthy that none of the 7 patients treated with penicillin alone showed resolution, whereas all 4 patients whose lesion resolved were treated with other drugs, namely carbomycin (1), erythromycin and streptomycin in combination (1), and COC (2). Four of the 5 patients who died received penicillin alone (3), or followed by other drugs. This must be interpreted in the light of the fact that 19 of the 24 patients received some form of penicillin and that in 18 of these, penicillin was the first drug prescribed. This would suggest that penicillin is not adequate therapy for Klebsiella pneumonia. Three of the patients who received penicillin for periods of 5, 7, and 15 days respectively, without clinical response, exhibited a fall in temperature within 72 hours

following the institution of COC therapy.

Certainly, penicillin alone remains the drug of choice in the treatment of pneumococcal pneumonias, but is of little or no value in the treatment of Klebsiella pneumonia. Furthermore, from the above data, it is apparent that COC is just as effective therapeutically as penicillin in the treatment of pneumococcal pneumonias and may be superior to its use alone in Klebsiella pneumonias. Also, as was true in one pneumococcal pneumonia patient in this series, occasionally a patient fails to respond to penicillin and COC may fill the need. It would seem, therefore, in the general practice of medicine, when the etiology of the pneumonia is not clear, that COC may prove a valuable substitute for penicillin under such conditions.

REFRACTORY URINARY TRACT INFECTIONS. Fourteen selected patients, suffering with refractory urinary tract infections have been treated with COC, 2 to 3 gm. daily in divided doses, the larger dosage being employed where *in vitro* tests suggested moderate resistance of organisms[5]. While most of the patients were treated for only 5 days, a few of the more severe cases received the drug for 7 to 10 days. In 5 patients there was complete disappearance of all bacteriological and clinical evidence of urinary tract infection, which had been refractory to previous medication. In 4 patients, there was complete disappearance of clinical evidence of the disease, but only temporary removal of the offending pathogen. In 3 patients, it was not possible to gauge clinical effectiveness because of the lack of characteristic signs and symptoms before therapy. In 2 of these, with mixed pathogens, the susceptible organism was eliminated, whereas the third was considered a therapeutic failure. Although the number of cases treated under controlled conditions does not permit a conclusive evaluation of the therapy and the follow-up period was of relatively short duration, the results herein reported suggest that COC has merit and is worthy of additional clinical study in the treatment of refractory urinary tract infections.

MISCELLANEOUS INFECTIONS. In addition to the above studies, COC therapy has been employed in the treatment of a number of other miscellaneous infections. Among these, have been single cases of typhoid fever[6] and Bacteroides empyema[2].

Typhoid Fever. At the time of admission, a 13-year-old boy complained of chills, fever, and watery stools of 7 days' duration. Blood and stool cultures were positive for S. *typhosa*. Specific treatment, started on the 15th day of the disease, consisted of COC, 0.5 gm. orally every 6 hours, which was followed in 36 hours by a definite clinical improvement, as manifested by a fall in temperature to within the limits of normal, cessation of chills, and a diminution in frequency of stools. On the 19th day of the disease (after 8 gm. of COC), blood, urine, and feces cultures were negative for S. *typhosa*. Therapy was continued until a total of 32 gm. of COC had been administered over a period of 16 days. There was no recurrence of clinical evidence of the disease or of positive cultures. While it is possible that the clinical result seen in this case could be attributed to the chloramphenicol (total 10.7 gm.) present in the combination, two facts are against it: (a) the total chloramphenicol dosage employed is much less than that recommended for successful treatment of typhoid fever and (b) inhibitory activity tests of the patient's serum against the homologous organism indicated that administration of an amount of chloramphenicol equivalent to that present in the

COC combination did not produce the same degree of either bacteriostatic or bactericidal activity as was produced by the combination[6].

Bacteroides Empyema. A 48-year-old male was admited with a 3-weeks' history of sharp pain in the right lower chest, fever, blood-streaked sputum, and a weight loss of 20 pounds. For a week prior to hospitalization, he had received varying amounts of penicillin intramuscularly. A thoracentesis, performed on the 5th day following admission, revealed a purulent exudate from which an anaerobic streptococcus and the Bacteroides were cultured. Two days later, the thoracentesis was repeated and the same findings were present. Initial therapy consisted of streptomycin, 1 gm. intramuscularly and procaine penicillin, 600,000 units intramuscularly, every 12 hours. This treatment was continued for 84 hours without clinical response. The patient was then given erythromycin 0.5 gm. by mouth for 48 hours, which likewise proved unsuccessful. On the 6th day following admission, he was given COC 0.5 gm. by mouth every 4 hours for 10 days. Thoracenteses were performed 7, 11, and 13 days following the institution of COC therapy and, with the exception of a coagulase-negative *Staphylococcus albus* in the first pleural fluid, following COC administration, all cultures showed no growth. Following the last thoracentesis, a rib resection and open drainage was performed. Postoperative antibiotic therapy consisted of penicillin and streptomycin for 10 additional days, following which, the patient made an uneventful recovery. Certainly, the rib resection and open drainage were important factors in this man's recovery. Nevertheless, the pleural fluid became sterile following the institution of COC therapy, which suggests its effectiveness in this type of infection.

Summary and Conclusions. 1. Extensive *in vitro* studies on the inhibition of various bacteria by single antibiotics, or in combination, indicate that a combination of chlortetracycline, oxytetracycline, and chloramphenicol possesses antibacterial properties which are not evident when these antibiotics are tested singly in equal concentrations against the same organisms.

2. Preliminary clinical studies indicate that a combination of chlortetracycline, oxytetracycline, and chloramphenicol is just as effective therapeutically as penicillin in the treatment of pneumococcal pneumonia and may be superior to its use alone in Klebsiella pneumonia. Furthermore, it has been shown that the combination COC has merit and is worthy of additional study in the treatment of refractory urinary tract infections. In addition, single cases of typhoid fever and Bacteroides empyema have likewise been successfully treated with the combination COC (chlortetracycline, oxytetracycline, and chloramphenicol).

3. Certainly, the status of antibiotic combinations in present day clinical medicine is still undetermined. This is largely due to the fact that not only is our knowledge of the mechanism by which each of these antibiotics exerts its activity *in vitro* very meager, but also our knowledge of their activity *in vivo* is even less. Therefore, in view of this lack of understanding of the mode of action of these drugs when used alone, it is impossible to predict empirically their action when used in combination. It would seem advisable, therefore, to keep an open mind and not to overlook the possible utility of antibiotic combinations until such time as sufficient evidence has been accumulated to indicate which combinations may, or may not, be useful. Certainly, we are justified in employing antibiotic

combinations clinically in those instances where appropriate laboratory tests fail to demonstrate definite antagonism.

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FAMILY STUDIES ON BRUCELLOSIS

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Although brucellosis is a human disease of major importance, man is not the obligatory host. Human brucellosis represents an example of what Theobold Smith[19] has called aberrant parasitism: man is not essential in the life cycle of the parasite. Several species of farm animals may serve as the reservoir, and at least three species of Brucella are responsible for animal and human disease. The most invasive of the three species is *Brucella melitensis*, and from a world point of view, this species is the most common cause of human brucellosis. In the United States the bovine variety, *Brucella abortus*, is of greater significance. While *Br. abortus* is the least invasive of Brucella organisms, it causes approximately three-fourths of the human cases in this country. Furthermore, the porcine variety, *Brucella suis*, causes more human disease in the United States than does *Br. melitensis*.

Several years ago my associates and I began a study of the natural history of human brucellosis. We were particularly interested in acquiring information on bacteriologically-proved cases due to *Br. abortus*, since such knowledge was incomplete. Table 1 is a summary of all the human cases that we have personally seen and studied over a period of 16 years, from 1937 to 1953. There is a total of 204 cases, of which 119 are culturally-proved cases. Almost 90% of the latter cases were due to *Br. abortus*. This number of abortus cases provided an excellent opportunity not only to study the clinical course of the disease, but also to investigate the epidemiological factors associated with the illness of each individual.

TABLE 1.—CASES OF BRUCELLOSIS STUDIED IN THE CLINICS OF THE UNIVERSITY OF MINNESOTA, 1937–1953

Culturally-proved cases		
Due to *Br. abortus*	102	
Due to *Br. suis*	12	
Due to *Br. melitensis*	5	
		119
Cases proved serologically, but culturally negative		85
Total		204

Since the epidemiological findings have revealed a much better understanding of the disease, the principal features may be summarized here. The reservoir of *Br. abortus* is mainly in cattle, and to a lesser extent in swine. In humans brucellosis is primarily a disease of males, with approximately

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three-fourths of the cases occurring in this sex, especially between the ages of 20 and 40 years. Brucellosis is chiefly an occupational disease with roughly three-fourths of the cases occurring in individuals who have had contact with infected animals or their immediate environment. For this reason, in our series the disease appeared most frequently in farmers and employees of meat packing plants. Not more than one-fourth of the cases resulted from the ingestion of contaminated raw milk. While children are commonly exposed to brucellosis, overt signs of the disease are unusual in those 12 years of age and under.

An investigation of the family unit has been quite revealing in the study of many communicable diseases, especially those diseases transmissible from man to man. It appeared that a family study of brucellosis would give needed information relative to the exposure rate, and to the problem of individual susceptibility to the disease. It was believed that such a study would emphasize further the insidious nature of brucellosis. Investigations in individuals having a febrile illness of doubtful etiology had demonstrated how easily brucellosis might have been overlooked if one were not on the watch for it, and if one did not utilize appropriate laboratory procedures for diagnostic purposes.

Before plunging into the details of the present study, brief reference should be made to the available knowledge on multiple cases of brucellosis arising from the same source. Since *Br. melitensis* is a much more invasive species than *Br. abortus*, the disease has been recognized frequently in epidemic form, and was brilliantly studied on the Island of Malta by the Commission on Mediterranean Fever[17]. *Br. suis* is also more invasive than *Br. abortus*, and it is significant that the major milk-borne epidemics of brucellosis in the United States have been due to *Br. suis* appearing in cow's milk[1,2,13]. Several excellent epidemiological studies involving institutions and communities where a large number of individuals have been exposed to *Br. abortus* occurring in a contaminated milk supply have emphasized the high exposure rate and the large number of individuals who became infected, but emphasis has also been placed upon the mildness of the disease and the relatively few who manifested evidence of illness[3,5-7,9,11,14,15,18,23-25]. In several of the foregoing reports passing reference has been made to more than one case of brucellosis occurring in a family, but detailed analyses of these family groups are lacking. In a classical study of brucellosis carried out by Hardy and his associates[10] in Iowa, attention was called to 10 instances in which more than one case appeared in the same household, but specific bacteriological data are absent in this report. In an extensive review of brucellosis in England, where *Br. abortus* is the etiology, Dalrymple-Champneys[4] found only 7 instances in which more than one case occurred in a household out of a total of 983 cases collected over a period of 22 years.

METHODS OF STUDY. Every patient with brucellosis examined in the clinics and hospitals of the University of Minnesota was interrogated with reference to the possibilities of exposure to the disease. Since multiple cases in a family would most likely occur in those instances in which a patient came from a rural area or from a farm where contact with diseased animals was possible, and where several members of a family might have ingested contaminated milk, further epidemiological information was obtained by interviewing and examining other members of these patients' families. In several in-

stances the family physician aided in our effort. Whenever possible, specimens of blood were obtained from each of the family group for cultures and for Brucella agglutination tests. In some instances, intradermal tests were performed with Brucella antigens in order to detect evidence of exposure to the disease.

Results. That brucellosis due to *Br. abortus* is a sporadic disease was clearly indicated by the fact that in a period of 16 years, during which time intensive epidemiological and clinical studies were carried out in an endemic area, there were only 9 families in which additional evidence of human infection was acquired. Eight of the 9 primary cases had positive blood cultures due to *Br. abortus*. While cultures in the ninth case remained negative, there was undoubted clinical and serological evidence of the presence of active disease. Although evidence of infection was present in 17 additional individuals coming from these 9 families, in no instance was there more than one additional case of illness in a family. These findings are summarized in Table 2.

TABLE 2.—SUMMARY OF FAMILY STUDIES

Total No. of Primary Cases—all with symptoms			9
With + blood cultures (*Br. abortus*)		8	
With 0 blood cultures		1	
Total No. Secondary Cases			17
With + blood cultures (*Br. abortus*)		4	
With symptoms	3		
Without symptoms	1		
With 0 blood cultures, but + aggls.		13	
With symptoms	1		
Without symptoms	12		

The mode of infection in these family cases has not been easy to determine, but the information at hand suggests that contact with infected animals and their contaminated environment may have been every bit as important as the ingestion of unpasteurized milk. Seven of the 9 families were living on farms on which there were herds of cattle with Bang's disease. While the members of these families did partake of unpasteurized milk from these animals, this fact does not exclude the importance of contact alone as being the source of their infections. In only one family was there unqualified evidence that the ingestion of raw milk was the sole source of the disease. The father of this family had acute brucellosis with a bacteremia due to *Br. abortus*. His occupation was that of collecting whole milk from various farms and delivering it to a creamery. One of the farmers supplied him with fresh, unpasteurized milk for his own family. Subsequently it was determined that this milk came from a herd of cattle with Bang's disease. This milk collector had a wife and two daughters, age 6 and 4 years. The 6-year-old child had a vague and mild type of illness. Her Brucella skin test was positive, and her titer of Brucella agglutinins was 1 to 1280. The wife and other daughter were well, and Brucella agglutinins were absent from their bloods.

The findings in the family of R. K. were of particular interest. The father was a 59-year-old farmer with acute brucellosis from whose blood *Br. abortus* was cultured. He had a herd of cattle with Bang's disease, and on occasions he had handled aborted material

with his bare hands, and had buried an aborted fetus. He and his family drank raw milk from this herd. His family consisted of a wife and five children, all of whom lived on the farm, and all of whom were in good health. However, blood specimens for agglutination tests and blood cultures were obtained from each member. One daughter aged 15 had an agglutinin titer of 1 to 160, and *Br. abortus* was cultured from her blood! An 8-year-old son had a titer of 1 to 160. It was apparent that 3 members of this family had acquired an infection, but only one had evidence of the disease.

ting of a father and a mother, and 6 brothers and sisters. This family possessed a small herd of cattle with Bang's disease, and all the members drank raw milk obtained from this herd. A veterinarian had told them that human beings do not acquire disease from cattle with Bang's disease. Intracutaneous tests and agglutination reactions were carried out on the 8 other members of her family. The results are presented in Table 3. Although illness was not present in any other members, there is evidence that at least 5 others in the family had been infected by Brucella. The 26-year-old

TABLE 3.—STUDIES ON FAMILY OF F. H.

(Bacteremia Due to *Br. abortus*)

Relation to Patient	*Age in Years*	*Skin Test (Protein)*	*Reciprocal of Agglutinin Titer*
1. Father	55	3+	160
2. Mother	54	2+	160
3. Brother	30	0	80
Patient	29	0	640
4. Sister	20	2+	160
5. Brother	18	1+	160
6. Sister	13	1+	80
7. Sister	26	0	0
8. Brother	22	0	0

A prominent and commonly encountered aspect of many communicable diseases is that several members of a family may be exposed to a disease, the tissues invaded, but apparent illness may be present in only a few of the infected individuals. That brucellosis is no exception to this concept was demonstrated in the family study just cited, and also in the family of F. H., a 29-year-old single woman living with her family on a small farm just outside of Minneapolis. She was seriously ill with brucellosis, *Br. abortus* having been isolated repeatedly from her blood. She was a member of a large and closely-knit family, consis-

sister with a negative intracutaneous test and absent Brucella agglutinins did not live at home, but only visited occasionally on weekends. Also, the 22-year-old brother without evidence of a past exposure lived at home but had only recently been discharged from the army.

We have had 3 father-son combinations in which *Br. abortus* was isolated from the 3 fathers and the 3 sons, and all 6 had evidence of active brucellosis. Because this is an unusual epidemiological finding in brucellosis due to *Br. abortus*, the data on these families will be briefly summarized.

Case Reports. CASES 1 AND 2. E. S., the father, was a 26-year-old white veterinarian, who specialized in obstetrics in large animals. He had had numerous attacks of brucellosis, the first occurring in 1943. He was ill in 1944 and 1945, and in good health in 1946 and 1947. In 1948, *Br. abortus* was recovered from his blood, and he had another attack in 1949. He recovered following antibiotic therapy.

Shortly after E. S. recovered, he brought B. S., his 3½ year old son, to the clinic because the boy had had fever, chills and walked with a limp. The father suspected that the boy might have poliomyelitis. But it was shown that he had acute brucellosis with an agglutinin titer of 1 to 2560, and *Br. abortus* was isolated from his blood on two occasions. The son recovered after appropriate treatment.

There were many possible sources of infection for the son. The father was closely attached to the boy and took him from farm to farm as he performed his daily duties. The boy was in barns where Bang's disease was present, and on several occasions a farm wife had handed him a glass of "nice fresh cow's milk"!

CASES 3 AND 4. M. H., a 36-year-old farmer, was in the hospital at the same time as his 12-year-old son, L. H. The father was quite ill with acute brucellosis. His blood had a Brucella agglutinin titer of 1 to 1280, and *Br. abortus* was isolated from a culture of blood. The son had had an attack of tonsillitis, which was followed by pains in his legs and weakness. He was suspected for some time of having acute rheumatic fever. But on the basis of his father's simultaneous illness, brucellosis was suspected and proved. The Brucella agglutinin titer of the son was also 1 to 1280, and *Br. abortus* was obtained from his blood.

This family had a herd of cattle with Bang's disease present. Additional members of the family included a wife and two other sons. Although the entire family consumed raw milk from the infected herd, the wife and the other two boys showed no evidence of having been infected.

CASES 5 AND 6. G. M., a 27-year-old single farmer, had been in the hospital for the treatment of a duodenal ulcer shortly before re-entering for acute brucellosis. He had a Brucella agglutinin titer of 1 to 1280, and his blood yielded *Br. abortus*. He lived with his father, who simultaneously developed a similar febrile illness. His physician upon learning the nature of his son's illness, submitted specimens of blood for brucellosis. The Brucella agglutinin titer was 1 to 800, and *Br. abortus* was recovered.

Both of these individuals living alone together were alcoholics. Both had duodenal ulcers, and both drank large quantities of raw milk obtained from cows with Bang's disease.

Concluding Remarks. This family study of brucellosis emphasizes a common feature of communicable disease in that a considerable number of individuals may be exposed to brucellosis, the tissues of many will have been invaded by the micro-organisms, but relatively few will manifest evidence of illness. We have encountered information of this nature in other groups. For example, of 1627 healthy donors of blood, mostly from rural areas, seen at the University of Minnesota Hospitals, 18.5% had Brucella agglutinins[21]. And in another survey in the out-patient department almost 20% of consecutive patients seen with a variety of complaints exhibited skin reaction to Brucella antigen[22]. Brucellosis can be properly called an occupational disease in meat-packing plants. While a considerable number of our patients have been employed in this industry, the cases have occurred sporadically. Considering the exposure rate, comparatively few men have presented evidence of the disease, although as Heathman[12] has pointed out, the tissues of many individuals have been parasitized without resulting illness.

Brucellosis as we have seen it, and as it exists in the United States, is an insidious disease. It causes a relatively benign type of illness compared to that due to *Br. melitensis*, and it occurs sporadically. All of these features of brucellosis due to *Br. abortus* may be related to the fact that this species is much less invasive than *Br. melitensis*. We have seen this difference in invasiveness expressed in illness contracted by laboratory personnel. Although

there has been more frequent exposure to *Br. abortus*, three people have had a bacteremia due to *Br. melitensis*, and one due to *Br. suis*, but we have never isolated *Br. abortus* from our personnel.

Finally, the present study and other epidemiological investigations that we have carried out accentuate the importance of contact with infected animals or their immediate environment in the acquisition of the disease, compared to the ingestion of contaminated milk as the cause of illness[16,20]. In our own experience, not more than one-fourth of all the cases are due to the latter cause. Why don't more people become ill from drinking raw milk? There are probably several factors responsible for the low incidence. One is a dilution factor in that at the distributing points for milk the Brucella organisms are diluted out so that only a small number of bacteria may be present in the milk. Another factor emphasized by Garrod[8] is that gastric juice has an extraordinarily high degree of bactericidal activity for *Br. abortus*. And then, we have been impressed by the individual susceptibility to the disease. Most individuals appear to tolerate exposure to small numbers of Brucella organisms without ill effects, but there is the occasional individual whose tissues are readily invaded, and disease results.

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CONTROL OF THE COMPLICATIONS OF DIABETES: HYPERGLYCEMIA AND GLYCOSURIA ENDOGENOUS AND EXOGENOUS INSULIN

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Many theories have been advanced to account for the crippling and vital involvement of the kidneys, heart, retinae and other organs, that have come to plague diabetics since their life span has been lengthened by means of injected insulin. None of these has proved to be fully satisfactory nor generally successful as a basis for the preventive therapy of the complications of diabetes. The present paper ventures some suggestions in this already overcrowded field.

PATHOLOGY OF DIABETES AND ITS COMPLICATIONS. It is obvious that the pathology of diabetes and its treatment have undergone revolutionary changes in the last 50 years. About 1900, 63.8% of diabetic deaths were due to coma, whereas in 1950, 75.9% were ascribed to cardio-renal-vascular disease; in addition the life span of the diabetic had been prolonged so as to approach the normal[9]. Reducing the incidence of coma to the vanishing point and lengthening the life of diabetics were wonderful achievements accomplished through the use of insulin. As the years passed, it became evident that we were dealing with entirely new problems: coronary disease, kidney involvement, retinopathy, and arteriosclerosis were the conditions afflicting the diabetic who lived longer. Dolger[2] called attention to the inevitable occurrence of these complications in those surviving 25 years of diabetes. On the other hand, Allen[1] has claimed and is claiming total freedom from all complications of diabetes when a normal blood sugar, that is, 150 mg. or less per 100 cc., is constantly maintained.

Warren and LeCompte[10] map out a tentative plan for the pathology of diabetes which is briefly summarized here. There is much evidence that this is partly or entirely correct, though a great deal of experimentation and observation remains to be done before it can be proved completely valid. However, in the author's opinion, it is the most acceptable scheme yet offered for the pathology of diabetes and provides a rational basis for the discussions which follow.

The accumulation of glycogen in the kidneys, heart, retinae, and the pancreas is regarded as the earliest demonstrable pathological lesion in diabetes and the first step in the development of complications. The deposit of glycogen in the kidneys is recognized as the most reliable and constant post-mortem finding diagnostic of diabetes. The abnormal concentration of glycogen is not static; it may be partly or entirely reversible or it may retrogress into degenerative changes. The inherent qualities of the tissues have a distinct bearing on the fate of glycogen deposited within them since the constant presence of glycogen in the liver and muscles does not engender degenerative processes.

Warren and LeCompte[10] point out that diabetes may be severe, yet the various organs be normal; however, even under these circumstances, insulin deficiency is demonstrated by the abnormal glycogen distribution.

Their final conclusion is as follows: "In summary, it appears that Friedenwald's concept may be extended to encompass all the major lesions characteristic of diabetes, in the sense that all of them involve either simple polysaccharides (glycogen), or polysaccharide complexes (mucopolysaccharides). The hypothesis is admittedly tenuous."

CAUSE OF DIABETIC COMPLICATIONS. Whether malnutrition, hyperglycemia, hypercholesterolemia, glycosuria or dessication, individually or collectively, were the reason for coma, cataract and infections before insulin was available for injection, and since then for the accumulation of large deposits of glycogen entailing permanent damage to the kidneys, eyes, heart and pancreas, the primary cause for any and all of these conditions must be sought for in the inadequacy of secreted, or of administered insulin. While the conservation of nutrition and keeping the urine free of sugar constituted the most that could be offered the diabetic for the control of diabetes both before and after the discovery of insulin, the management of this disease presents entirely new problems. In the past, hyperglycemia, glycosuria, polyuria, dessication and malnutrition were mostly unavoidable, even with very low diets, and early death from coma or malnutrition and development of cataract were the rule. With the introduction of insulin, deaths due to these causes were eliminated, as was cataract. Hyperglycemia, glycosuria, polyuria and dessication appeared to be responsible factors. With the use of insulin, in striving to prevent the occurrence of complications in diabetes, slight amounts of sugar in the urine are usually disregarded, large amounts condoned by the free dieters, and complete absence of sugar in the urine insisted on by others. It becomes clear that there are two phases of the problem concerning the therapy of diabetes that may be singled out for discussion, the first being applicable to the era preceding the discovery of insulin, that is, when hyperglycemia, glycosuria and dessication were almost inevitable, the second concerning the period when the work of Banting and Best produced insulin, comprising about 30 years, during which the replacement of lack of the body's own insulin by injection of insulin derived from animals, exogenous insulin, controlled the former problems but failed to yield a complete cure.

HYPERGLYCEMIA AND DESSICATION. Mosenthal[4] (1935), largely by clinical observation and gathering the available evidence, demonstrated that hyperglycemia, in the absence of glycosuria, did not depress immunity to infections, tissue growth, or the power to repair damaged tissues, and appeared to be a permissible infraction of normality in diabetics. Insulin had been available for a comparatively short time, and the prominence which nephritis, retinitis and coronary thrombosis would assume after the prolongation of the life of diabetics through its use, was not then appreciated. Most physicians and scientists agreed to this reasoning. There were some exceptions, notably the stand assumed by Allen[1], who in many discussions and articles, has called for perfect control: that is a normal blood sugar level constantly maintained at 150 mg. or less per 100 cc., and freedom from glycosuria. It is only recently that I have come to realize that Allen and I were advocating approximately the same standards for control, since Mosenthal and Barry[5], established that the renal threshold to glucose was at a level of 200 mg. per 100 cc. of arterial blood, which, after meals at least, is about the same as 150 mg. per 100 cc. in venous blood. Furthermore, an arterial blood sugar above

200 mg. can be very readily detected in the urine, whereas short of analyzing the blood every half hour one could not be certain about the height of the venous blood sugar.

Richardson[6] showed that immunity depended upon the glycogen content of the liver rather than upon the blood sugar level.

The principal defect responsible for the pre-insulin complications of metabolism in diabetes appeared to be dessication which depends upon the cyclical development of an elevated blood sugar, glycosuria and polyuria[4].

A complete, or almost complete, lack of insulin results in depletion of liver glycogen and the accumulation of glycogen in the extrahepatic tissues. The formation of glycogen is known to be a usual step in the utilization of glucose. In the absence of insulin the liver does not transform glucose either to glycogen or to fat, so that all of the food absorbed as glucose and all of the glucose formed by the liver from lactic acid and from protein fragments passes into the bloodstream as glucose. (This state of affairs, often spoken of as overproduction of glucose by the liver, would be more appropriately designated as lack of the liver's ability to retain glucose). A blood sugar level of about 350 mg. per 100 cc. serves to stimulate the tissues to a normal degree of sugar utilization, even though insulin is lacking (Soskin and Levine[7]) and as part of such vicarious utilization of glucose, the extrahepatic tissues, which ordinarily contain no glycogen, come to harbor a considerable amount of this material. Although such accumulations of glycogen often are reversible, apparently some of them undergo degenerative changes that leave their irreducible trail in the course of years (Warren and Lecompte[10], Dolger[2]).

INSULIN, ENDOGENOUS AND EXOGENOUS. A difference exists between the effect of endogenous: the body's own insulin, and exogenous: injected insulin.

Stadie[8] established the fact that insulin in the circulation was not affected by the blood cells but formed a stable yet potentially active combination with the first tissue with which it came in contact.

Endogenous insulin originates in the pancreas, passes through the portal vein to the liver where it makes its primary contact with tissues cells. Because of the size of the liver and the high concentration of insulin in the portal vein, probably the greater part of the insulin is bound here and only a comparatively small portion passes into the veins for general distribution.

Injected, exogenous insulin, given subcutaneously, is absorbed by the capillaries and flows through the veins and lungs to the arterial system. A study of radioactive insulin on intravenous injection has shown that in the tissues studied the greatest concentration of insulin is found in the kidneys, next in the thyroid and least in the liver: a distribution corresponding closely to the amount of blood flowing through the arteries to these organs[3]. Another point that might be noted about exogenous insulin is that with its great concentration in the kidneys, it naturally follows that a considerable quantity of the insulin is lost in the urine. In either case, with the endogenous or exogenous insulin, a certain amount of this hormone may be found to escape combination with the tissues and be present in the blood.

The insulin liberated during fasting or between meals, whether of endogenous or exogenous origin, may be regarded as "basic insulin". In addition, normal individuals possess the faculty of secreting "extra insulin" by the pancreas when the blood sugar in

the pancreatic artery rises. This extra insulin passes via the portal vein to the liver where it combines with liver tissue, serving to assimilate, as fat or glycogen, any sugar subsequently brought to it from the intestine. This extra insulin serves to confine postprandial blood sugar rise in normals to a half hour after meals, though in diabetics even with a normal fasting blood sugar, the postprandial blood sugar rise continues for 4 hours at least. The inability of the diabetic to furnish extra insulin while being treated with exogenous insulin, has been pointed out as an irremediable defect of injected insulin. This is correct, unless the diet is so low in carbohydrate that a postprandial increase in blood sugar is completely avoided.

When the liver contains large stores of insulin, as it does when endogenous insulin predominates, there will be only limited postprandial elevation of the blood sugar or none at all; but when exogenous insulin is resorted to, the postprandial rise in blood sugar will be marked and prolonged. At first we sought this matter only in the 1-hour up to 4-hours after meals in normals, and found no rise in blood sugar: this has been substantiated by various investigations of this subject. However, in many of these same publications a rise of blood sugar was recorded at the half-hour interval after the taking of meals. We checked this matter and found that in normals a rise in blood sugar occurred in the half-hour postprandial interval, but only when sugar

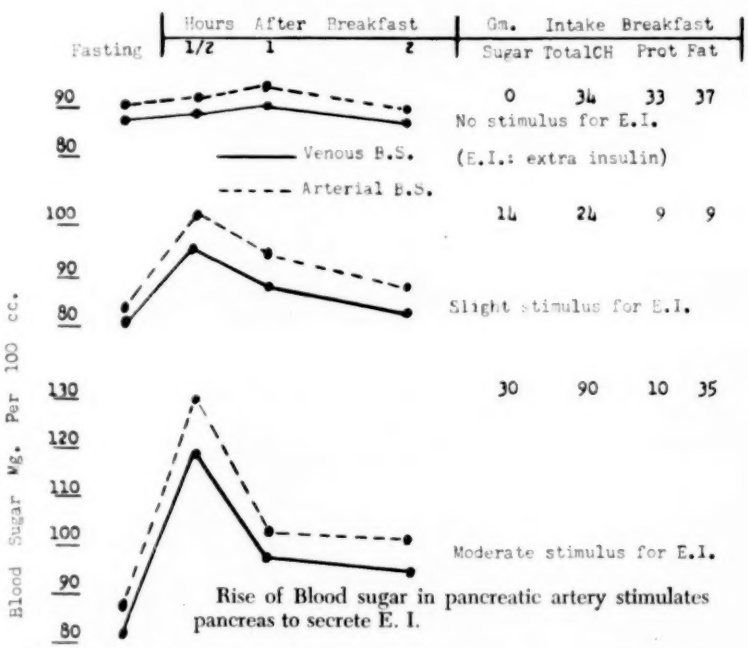

Chart 1.—Postprandial Blood Sugar in Normals. Only 3 of a number of results are charted. It is evident that: 1. The maximal rise of blood sugar occurs ½ hour after breakfast. 2. Within 1 hour postprandial, certainly within 2 hours, the blood sugar returns to basic levels. 3. The postprandial rise of blood sugar is directly proportional to the amount of sugar ingested.

was taken. When no sugar was eaten, either as sugar or in fruit juice, the rise of blood sugar failed to materialize (Chart 1). This makes it certain that the ingestion of sugar is responsible for the elevation of the blood sugar occurring within half an hour after eating. This curve closely resembles that obtained in normal glucose tolerance tests.

The lack of rise of blood sugar after the eating of food in normals, from

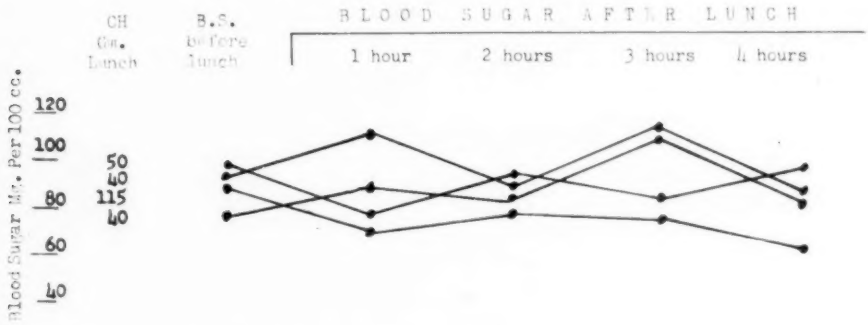

Chart 2.—Four normals. Blood sugar (arterial) after lunch remains constant, there is no rise. Observations begin 1 hour after lunch. Arterial blood sugar only charted. The venous blood sugar was also carried out, but the A-V difference was so slight that the interpretations of the results were not affected. The same statements apply to Charts 3 and 4.

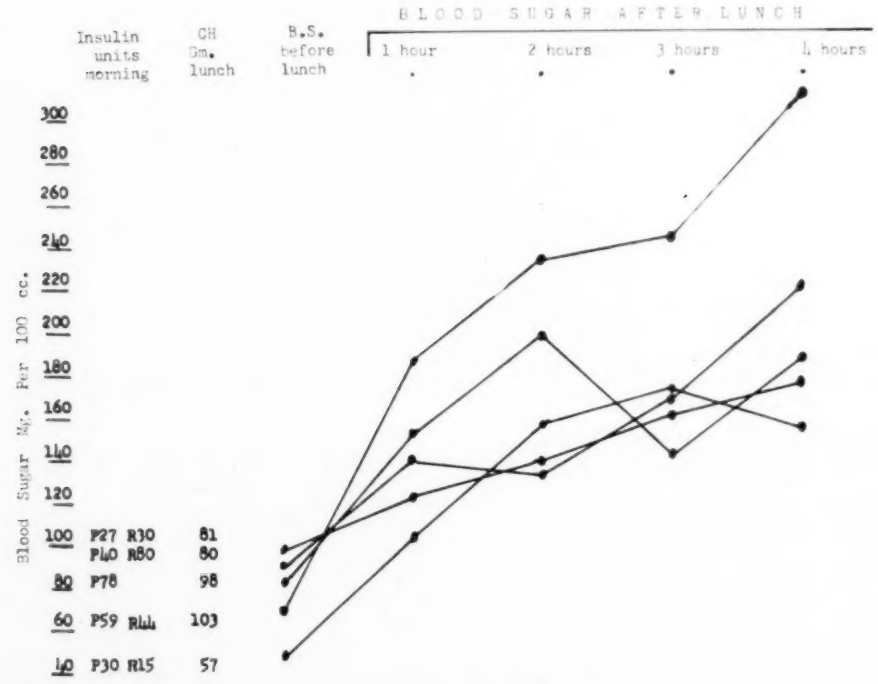

Chart 3.—Five diabetics receiving insulin, with normal blood sugar before lunch, all had a rise of blood sugar after lunch.

one to four hours, may be seen in Chart 2. In diabetics when the fasting blood sugar is at a normal level, there is an immediate and prolonged rise in blood sugar for a period of more than 4 hours (Chart 3). When the fasting blood sugar is high, then the postprandial rise in blood sugar assumes a bizzare picture (Chart 4). Charts 2, 3 and 4 are all of arterial blood sugar. They did not show any great arterio-venous difference so that the venous blood sugar has been omitted.

We have established the fact that the renal threshold to glucose is at a level of about 200 mg. of arterial blood sugar per 100 cc., and it is seen in diabetics receiving insulin, that when the

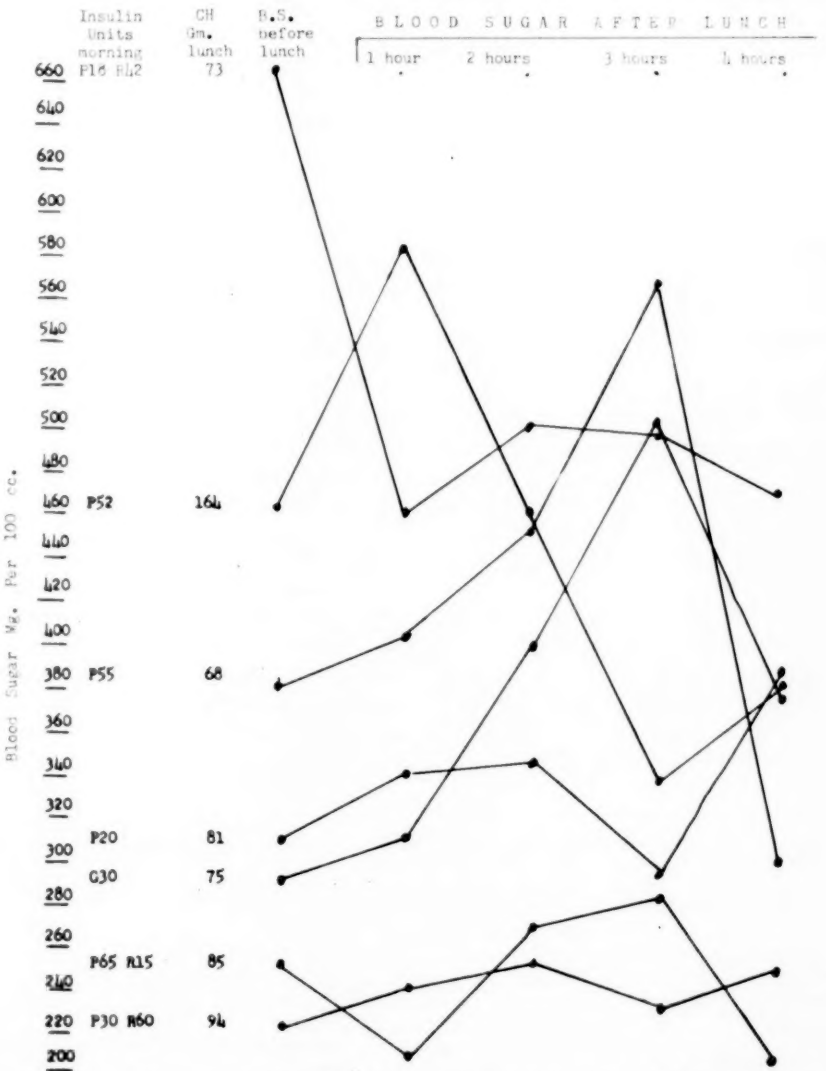

Chart 4.—Seven diabetics receiving insulin, with an elevated blood sugar before lunch. In three, blood sugar remained fairly constant. In three blood sugar rose, then dropped appreciably. In one, blood sugar dropped markedly and then remained constant.

fasting blood sugar is normal the sugar scarcely ever rises above that point after meals (Chart 3). However, when the fasting blood sugar is high (Chart 4), then the blood sugar attains a level very distinctly above 200 mg. per 100 cc., and it may be presumed that a considerable glycosuria has been generated. It may be noted that the blood sugar does not rise constantly, as in the patients with a lower initial blood sugar (Chart 3), but that it fluctuates a great deal. This fluctuation may be ascribed to the loss of sugar in the urine and also to the possibility of the high blood sugar resulting in an extensive vicarious utilization of sugar and glycogen accumulation by the tissues. Such glycogen deposits, as previously discussed, are the probable cause for the diabetic complications in the kidneys, retinae, heart and the pancreas so frequently present in diabetics that have had their disease for a considerable number of years.

Summary and Conclusions. The role of the liver in diabetes is more rationally conceived as lack of ability to assimilate and retain glucose as glycogen and fat, rather than overproduction of glucose.

Before insulin was available by injection, diabetics did not live very long, the majority of deaths being due to coma or infection which resulted from a persistent hyperglycemia, glycosuria, polyuria and dessication.

Since the introduction of insulin diabetics live much longer and coma has virtually disappeared as a cause of death. The development of nephritis, coronary thrombosis, retinitis and arteriosclerosis appeared almost inevitable after 25 years of diabetes. According to Warren and LeCompte[10], the deposit of glycogen in the kidneys, heart, retina, and arteries, resulting from persistent hyperglycemia, and not always reversible, is the cause of such degenerative changes.

Insulin, administered by injection, is not the complete remedy for diabetes, because the greater part of the injected insulin acts in the extrahepatic tissues and results in the deposit of glycogen in them. In addition to an insulin with prolonged action, a diet containing no free sugar and a regular amount of slowly absorbable sugar (starches and, to a lesser extent, proteins) so as to adjust itself to the limited amount of insulin harbored in the liver and to prevent an inordinate postprandial rise of blood sugar, would appear to be the answer.

The "free diet" plan, though it prevents death from coma and malnutrition, does not meet the demands of the present, well-founded belief regarding the cause of diabetic involvement of the kidneys, retinae, heart, pancreas, arteries and possibly other structures.

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PYRIMIDINE METABOLISM IN DIABETES MELLITUS STUDIED WITH N^{15} LABELED URACIL

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The discovery of the experimental production of diabetes by alloxan in man and animals has led to the suggestion of its possible involvement in the pathogenesis of diabetes mellitus[7,8]. This was first investigated by attempts to demonstrate the presence of alloxan as a natural metabolite in the body. Despite the sensitive analytical methods available, its presence has not been demonstrated unless the drug itself has been administered[1]. A reason for this may be found in the recent work of the Seligsons[15] who showed that alloxan is rapidly converted to alloxanic acid when added to the plasma.

Alloxan is one of the class of compounds known as pyrimidines, which with purines are basic components of the nucleic acids. Nucleic acids are found in both the nucleus and cytoplasm of all cells and so constitute the major metabolic pool of pyrimidines. Cerecedo[5] showed by balance studies in dogs that the pyrimidine uracil is metabolized to urea (Fig. 1). That this is the major sequence in the degradation of uracil in man has also been shown in studies with uracil labeled with isotopic nitrogen[4].

An intermediate in this series of reactions is isodialuric acid. A comparison of the structural formulae of alloxan and isodialuric acid demonstrates their relationship (Fig. 2). These compounds differ only in the state of oxidation of the carbon atom at position 4. Thus alloxan may be considered as an oxidative product of isodialuric acid. This suggests a possible mechanism for alloxan formation during pyrimidine metabolism under special circumstances favoring oxidation of the carbon atom at position 4 rather than the carbon atoms at positions 5 and 6 which would produce formyl oxaluric acid.

Even very small amounts of alloxan slowly formed by such a metabolic process may act on the islets of Langerhans over a long period of time to produce gradual transition into the diabetic state rather than the sudden acute picture which results when alloxan is administered intravenously. Repeated small sub-diabetogenic doses of alloxan given over a long period of time diminish islet cell function as shown by alteration in glucose tolerance tests without causing overt diabetes[17]. Thus, in the diabetic individual an error of pyrimidine metabolism may occur at the isodialuric acid stage with the production of alloxan or an alloxan-like substance which in turn affects the beta cells of the islets of Langerhans to produce diabetes. Instead of isodialuric acid proceeding along the normal route of metabolism to urea, alloxan

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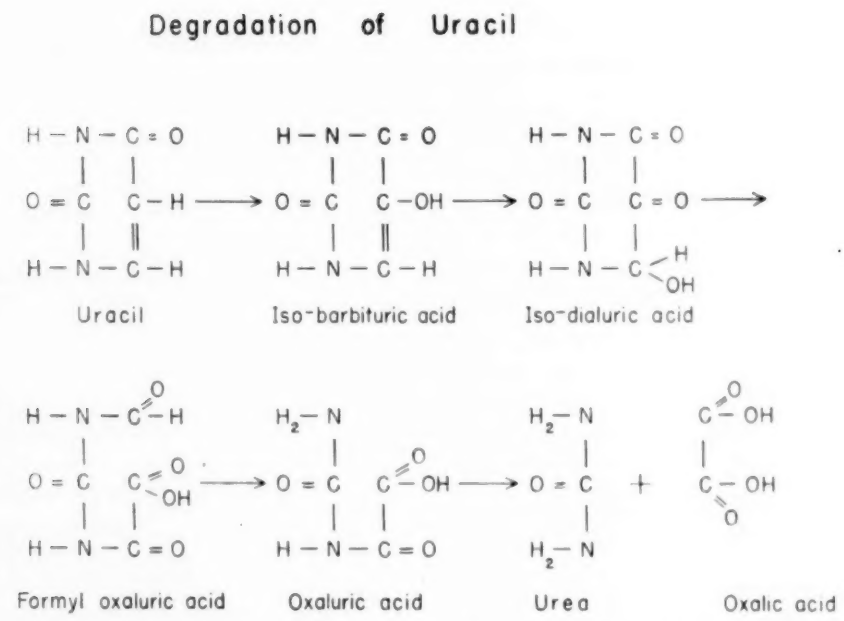

Fig. 1.—Scheme for the degradation of uracil to urea as proposed by Cerecedo[5].

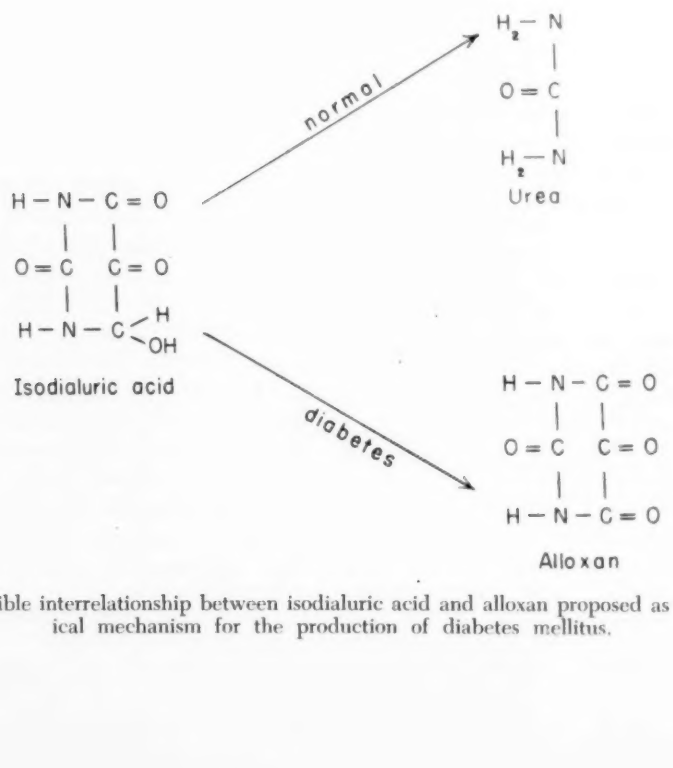

Fig. 2.—Possible interrelationship between isodialuric acid and alloxan proposed as a hypothetical mechanism for the production of diabetes mellitus.

may be formed in an abnormal side reaction.

In a previous paper we presented data confirming Cerecedo's work in man[4]. It was shown that the pyrimidine, uracil, labeled with the heavy nitrogen isotope (N^{15}) was metabolized to urea when given intravenously to a normal subject. It is the purpose of this series of studies to investigate the possibility that, during the metabolism of the pyrimidines in patients with diabetes and those with a diabetic predisposition, some metabolic error occurs, such that a portion of the metabolic pool of pyrimidines does not undergo the normal route of degradation but is oxidized to alloxan or an alloxan-like material instead. In the present report results following the intravenous infusion of isotopic (N^{15}) uracil into a diabetic man are given. In comparing the manner in which the uracil was metabolized in the diabetic and the normal patient, a difference in pyrimidine metabolism is demonstrated which gives some support to the above hypothesis and may provide clues to other avenues for investigating the problem.

Methods. The subject was a 29-year-old white male with an 8-year history of diabetes mellitus. His renal function was good and there was no pulmonary or cardiac disease demonstrable. He was hospitalized and had been receiving 40 units of NPH insulin daily prior to the period of observation. Insulin and all other medication were discontinued during the entire period of study. He was given a low purine diet of 2400 calories during the experimental period. Fasting blood sugars showed him to be hyperglycemic. All urines contained 4 + glucose, but were free of acetone during the entire period of observation.

The previously described protocol[4] was followed with a few minor variations. A 24-hour urine was collected as a control, and the subject was then given 205.3 mg. of isotopic uracil containing 32.1 atom % excess N^{15} intravenously over a 15-minute period. Urine specimens were collected at 8, 24, 48 and 72 hours following the infusion.

The N^{15} uracil was synthesized and prepared for intravenous administration as previously described[4]. Total nitrogen, urea, and uric acid were isolated and the isotopic abundance of heavy nitrogen was determined in each sample of urine[4]. In addition, the ammonia of each urine specimen was isolated and its N^{15} abundance determined[3]. Quantitative total nitrogen, urea, and uric acid determinations were done on all urine samples.

Results. Table 1 shows the urinary excretion of N^{15} as urea, uric acid and total nitrogen. The results indicate that a large portion of the administered uracil was metabolized to and excreted as urea. There was a progressive decrease in the isotopic abundance of N^{15} in the urea and total nitrogen fractions. Twenty-seven per cent of the N^{15} given was excreted as urea in 8 hours as compared to the 12% previously found in the normal man[4]. From 8 to 24 hours only 15% appeared as urea while in the normal the greatest excretion of N^{15} occurred in the 24-hour fraction.

The atom per cent excess N^{15} of the total urinary nitrogen exceeded that of the urea during the first 8 hours but was the same at 24 hours. At no time did the atom per cent excess N^{15} of the urea exceed that of the total nitrogen.

This may be interpreted to mean that during the first 8 hours a substance or substances containing N^{15} in higher isotopic abundance than that in urea was excreted. At the end of 24 hours, the atom per cent excess N^{15} of the urea and total nitrogen were the same. This suggests that the N^{15} containing substance(s) may have continued to be excreted as a part of the total nitrogen fraction but in either negligible concentration as compared to the 8-hour specimen or with an isotopic abundance of N^{15} which approximated that of the urea. If urea had been the

only N^{15} containing substance excreted, its atom per cent excess N^{15} would have been greater than that of the total nitrogen since the nitrogenous substances in the urine which did not contain N^{15} would have acted as a diluent to decrease the isotopic abundance of N^{15} found on total urine nitrogen analysis. The fact that the atom per cent excess N^{15} of the total nitrogen at 8 hours exceeded and then at 24 hours only equalled that of the urea, is evidence that the excretion of the other N^{15} substance (or substances) fell off at a more rapid rate than did the urea from 8 to 24 hours.

Between 24 to 48 hours (at about 30 hours) more N^{15} was excreted in the urine. This is in contrast to the normal man who continued to excrete it for 72 hours[4]. The atom per cent excess of N^{15} in each specimen studied was less in the diabetic when compared with the corresponding specimen from the normal man. This may be accounted for by the greater dilution of N^{15} since almost twice as much nitrogenous substances were excreted in the urine of the diabetic. He did not receive insulin during the experiment and thus a greater breakdown of protein should be expected. Approximately 50% of the administered N^{15} was recovered during the course of the experiment.

Table 1 shows an increase over control values in the atom per cent excess N^{15} in uric acid in the 8-hour urine specimen. This occurred only in the 8-hour specimen. In all the others there was no increase over the normal N^{15} abundance. This would indicate that except for the finding in the 8-hour urine specimen, uracil did not measurably metabolize to uric acid. Unfortunately, we were unable to recheck this value for lack of sufficient volume of sample. However, if the 8-hour value is significant it would indicate that about 0.06 mg. of N^{15} appeared in the 8-hour uric acid fraction. This would constitute only about 0.39% of the administered N^{15}. The significance of this result is questionable, for if uracil were metabolized to uric acid the excretion of N^{15} labeled uric acid for only 8 hours with abrupt cessation at this point is not readily explained. It has been shown that intravenously administered N^{15} uric acid continues to be excreted for several days[10].

TABLE 1.—URINARY EXCRETION OF N^{15} AS TOTAL NITROGEN, UREA AND URIC ACID FOLLOWING THE INTRAVENOUS ADMINISTRATION OF 205 MG. OF N^{15} URACIL CONTAINING 16.3 MG. OF ISOTOPE.

	Total Nitrogen			*Urea Nitrogen*			*Uric Acid Nitrogen*		
Time Hours	*Atom % Excess N^{15}*	*mg. N^{15}*	*% of dose N^{15}*	*Atom % Excess N^{15}*	*mg. N^{15}*	*% of Dose N^{15}*	*Atom % Excess N^{15}*	*mg N^{15}*	*% of Dose N^{15}*
Control	0	0	0	0	0	0	0	0	0
8	0.071	5.24	32.1	0.060	4.42	22.0	0.033	0.06	0.39
24	0.022	2.77	17.0	0.022	2.53	15.5	0	0	0
48	0.004	0.76	4.6	0.001	0.16	0.9	0	0	0
72	0	0	0	0	0	0	0	0	0
Total			53.7			38.4			0

Table 2 shows the excretion of N^{15} as urinary ammonia. Only the 8 and 24-hour specimens contained measurable amounts of N^{15} indicating that some of the uracil was metabolized to ammonia. As was the case for urea N^{15}, the excretion of isotopic ammonia in the urine of this diabetic patient persisted no longer than 24 hours.

TABLE 2.—URINARY EXCRETION OF N^{15} AS AMMONIA FOLLOWING THE INTRAVENOUS ADMINISTRATION OF 205.5 MG. OF ISOTOPIC URACIL 32.1 ATOM % EXCESS.

Time	*Atom % N^{15}*
control	--
8 hours	0.114
24	0.039
48	0
72	0

The atom per cent excess N^{15} of the ammonia was about 2 times greater than that of the urea or total nitrogen in the 8 and 24-hour fractions. This finding would indicate that ammonia appears earlier in the sequence of the steps in the degradation of uracil than urea. This is also evidence for the existence of a route for the degradation of uracil to ammonia in addition to that (Fig. 1) proposed by Cerecedo[5] which results in urea. Indeed, Cerecedo's scheme may require modification since the ammonia formed could contribute to the precursor pool for urea.

Discussion. This work shows that a large portion of exogenous uracil is metabolized to and excreted as urea in the diabetic. When the rate of excretion of N^{15} urea is compared to that found in the normal man[4], it is evident that uracil is much more rapidly metabolized by this route in the diabetic not receiving insulin. Almost twice as much of the administered uracil N^{15} appeared as urea in the 8-hour urine of the diabetic as did in the corresponding specimen of the normal man. This occurred even though the total urea output by the diabetic was considerably greater than that of the normal individual.

If increased catabolism of exogenous uracil is a measure of increased catabolism of endogenous pyrimidines, and this in turn indicates a more rapid breakdown of nucleic acids, one may conclude that there is a greater catabolism of nucleic acids in the diabetic than in the normal. Increased catabolism of proteins in the untreated diabetic has been shown to occur since urinary nitrogen excretion is greatly increased as was found in this patient. It is conceivable that during the course of increased nucleo-protein catabolism the nucleic acid groups could be split off and not undergo any further breakdown or their rate of degradation could be much slower. However, the data show that all of the uracil that could be accounted for as urea was excreted by the end of 48 hours after administration, in contrast to the 72 hours required to account for about the same per cent in the normal man. This seems to indicate that the increased pyrimidine breakdown paralleled the increased protein catabolism in the diabetic.

Only about 50% of the administered N^{15} could be accounted for in the urine of both the normal and the diabetic even though the rate of catabolism was more rapid in the latter. Either the N^{15} was excreted by another route or routes or it entered into the metabolic pool of perhaps ammonia in such a fashion that it did not readily appear in the urine.

All statements refer to exogenous pyrimidine metabolism only. It is possible that endogenous pyrimidines may undergo a different route of catabolism.

The pattern of urinary excretion of total N^{15} and urea N^{15} suggested that

an additional N^{15} containing substance(s) was excreted during the first 8 hours and then at a lesser rate from then on until 24 hours. This was in marked contrast to the pattern of excretion of N^{15} found during the first 24 hours of a normal man following the intravenous administration of uracil[4]. In the normal the pattern of excretion was the same during the first 8 hours, but from then on a reversal occurred and the atom per cent excess N^{15} of the urea exceeded that of the total nitrogen. This was taken to indicate that the additional N^{15} substance(s) was only excreted for the first 8 hours and then was no longer present in measurable amounts. In the diabetic patient the additional N^{15} substance(s) continued to be excreted until 24 hours or as long as isotopic nitrogen appeared in the urine.

In the case of the normal man it was thought that the additional N^{15} substance(s) was unchanged uracil. If the same interpretation is applied in the present study, it would appear that the diabetic man continued to excrete unchanged uracil or some other substance for a much longer period of time even though the rate of breakdown of metabolized uracil was more rapid. A definite conclusion cannot be drawn as to the true identity of the other N^{15} containing substance(s) and must await further investigation. A strong possibility exists that it may be merely ammonia.

If an alloxan or an alloxan type substance were formed as a result of a disorder of pyrimidine metabolism, one would expect it to be metabolized and excreted differently than the other pyrimidines found in nucleic acids on the basis of previous work. In balance experiments on dogs, Cerecedo showed that alloxan did not metabolize to urea and was unlike the other pyrimidines in this respect[6]. Lee and Stetten used N^{15} alloxan and alloxan labeled with radio-active carbon (C^{14}). They found very little metabolized to urinary urea in rats and rabbits. The isotopes were excreted in the urine as an unidentified substance. About 62% of the total isotope (N^{15} or C^{14}) was accounted for in the urine over a 3-day period[11]. In previous work by Plentl and Schoenheimer, the same species of animals were shown to convert pyrimidines found in nucleic acid to urea[13]. Consequently, if an alloxan type of substance was formed during the catabolism of uracil in this diabetic patient, one would expect to find more uracil to be excreted as the unidentified N^{15} containing substance(s). The data indicates that the diabetic patient excreted the unidentified substance over a much longer period of time than did the normal man, even though the rate of pyrimidine catabolism was increased.

An alloxan-like substance could be produced in very small amounts over a long period of time which might result in the picture of gradual impairment of beta cell function of the islets of Langerhans seen clinically. Actual destruction of the beta cells would not have to occur in order for their insulin-producing function to be impaired. Impaired function of a cell does not necessarily require visible morphologic change. It is well known that only about 25% of all diabetics show morphologic changes of the islets of Langerhans at necropsy. If the altered pyrimidine metabolism were severe enough to produce large amounts of a toxic substance which persisted for a long enough period of time, actual morphologic changes of the islet cell tissue could occur.

It is unlikely that the unidentified N^{15} substance could be alloxan, for it has

been shown by Seligson and coworkers that alloxan cannot be found in the plasma even when it is added[15]. It is rapidly converted to alloxanic acid. These workers showed that oxomalonic acid which arises from the degradation of alloxanic acid does occur in the urine of normal and diabetic people suggesting that alloxan may be a precursor.

Isotopic nitrogen appeared only in the 8-hour uric acid specimen, the others were free of N^{15}. According to our calculations this only amounted to about 0.06 mg. of N^{15}. If some of the uracil did metabolize to uric acid during the first 8 hours, it is difficult to understand why it abruptly ceased to be excreted at that time. The excretion would be expected to taper off more gradually in view of the work of others[2] who have shown that intravenously administered N^{15} uric acid was excreted slowly over a period of days.

A very interesting observation was the appearance of N^{15} in high concentration in the urinary ammonia of the 8 and 24-hour specimens. This confirms Plentl and Schoenheimer's findings in rats and indicates that the exogenous pyrimidines are a source of urinary ammonia. It is evident that the N^{15} ammonia was not formed from the breakdown of the isotopic urea since it has been shown that once urea is formed it is stable and is not a source of urinary ammonia[12]. This is further borne out by the fact that the atom per cent excess N^{15} of the ammonia was two times as great as that of the total nitrogen and urea.

This means that a portion of the uracil may have metabolized along a different route consisting of deamination and cleavage of the pyrimidine ring with the formation of ammonia. This could either be combined with glutamic acid to form glutamine and then split off by the kidney and excreted as ammonia or go on to form urea via ammonia as happens with amino acid nitrogen. Thus, the pyrimidines may be metabolized to urea by more than one method: (1) cleavage of the ring with the retention of the urea portion as put forth by Cerecedo[5] and (2) the deamination method as described above. The latter method could also account for some of the pyrimidines being excreted as substances other than urea and ammonia, such as beta amino isobutyric acid[9] and CO_2. Rutman *et al.*[14] have recently shown in rats that the ureido carbon of uracil labeled with radioactive carbon (C^{14}) was converted to expired $C^{14}O_2$ indicating that the second route is a distinct possibility.

It is realized that great caution must be exercised in interpreting these data as the above findings could be ascribed to a lack of insulin and not really reflect a basic metabolic defect of pyrimidine metabolism. It is also realized that the results may represent individual variation between two people rather than a true metabolic difference. These studies are in progress on more patients with a view towards more soundly establishing these differences.

Summary. A hypothesis was advanced which assumes that diabetes mellitus may result as an error of pyrimidine metabolism which produces an alloxan-type substance at the isodialuric stage of the degradation of uracil. This would in turn affect the insulin producing cells of the pancreas to cause diabetes.

The pyrimidine uracil was synthesized with isotopic heavy nitrogen (N^{15}) and administered intravenously to a diabetic who did not receive insulin during the course of the study. The metabolism of the uracil was compared

with a similar previous study in a normal man. It was shown that the uracil was broken down much more rapidly to urea in the diabetic than in the normal. However, only about 50% of the administered N^{15} was recovered from the urine in both cases in the 72-hour period of investigation. An unidentified N^{15} containing substance was excreted by the diabetic for a much longer period of time, 24 hours as compared to 8 hours for the normal. The urinary ammonia of the diabetic was found to contain the largest atom per cent excess of N^{15} in the nitrogenous compounds which were identified in the urine.

The relation of the results of this study to the above hypothesis were discussed. The possibilities of uracil being broken down to urea by more than one route and that it might give rise to more end products than urea and ammonia were also discussed.

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PORTAL CIRRHOSIS: CORRELATION BETWEEN THE SEVERITY OF ESOPHAGEAL VARICES AND VARIATIONS IN PHYSICAL FINDINGS

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The limited knowledge of the natural history of esophageal varices constitutes a serious hiatus in understanding the patient with cirrhosis, and this is a matter of considerable concern to those who assume responsibility for the surgical treatment of varices. Information is lacking on the stability of varices, particularly as to whether their size and extent might spontaneously be affected from time to time by utilization of other natural collateral portacaval systems. If it should be that varices are not static under conditions of relatively static portal hypertension because there is variation in the volume of portal blood they are called upon to carry, rather radical alteration might have to be made in one's thoughts on indications for surgical therapy and on evaluation of the results of surgical decompression. A previous study[4] indicated that changes in size and extent of esophageal varices secondary to portal cirrhosis do not necessarily parallel changes in the severity of the cirrhosis or its secondary effects. It was found that evaluation of the severity of varices by a single esophagoscopic examination could, as a consequence, be misleading. A second investigation[3] showed that there is imperfect correlation between changes in portal venous pressure and changes in the severity of varices. It was concluded that enlarging varices are not necessarily an indication of rising portal pressure and that portal pressure cannot be estimated from varix severity. Recently, Dye and colleagues[2] described 11 cases of cirrhosis which seemed to demonstrate improvement in portal hypertension following varying periods of medical treatment.

The present study was initiated in an effort to evaluate another factor which requires correlation with severity of varices, the simple clinical features which may accompany portal hypertension. In particular, it appeared important to determine whether changes in physical findings may be relied upon to give indirect evidence about the course of varices.

Material and Methods. Sixty patients with portal cirrhosis and esophageal varices were studied. The diagnosis of cirrhosis had been proved by liver biopsy at the outset of each case study. None of the patients had had any operative or manipulative procedure to reduce portal hypertension or to obliterate the varices. Fifty-two of the subjects were men. The ages varied from 22 to 64 years. Some patients were receiving in-patient cirrhosis therapy, and others were being followed as out-patients on prescribed regimens.

For reasons previously explained[1], all evaluations of varix severity were made by esophagoscopic inspection. Some of the patients were examined esophagoscopically more than twice; a total of 135 examinations was made. Evaluation was based on two features: the

extent of the esophagus involved by varices, and the diameter of the varices in the esophageal segment most severely involved. The former was measured on the portion of the esophagoscope protruding beyond the alveolar ridge when the most proximal varix was encountered. Varix diameter was measured directly under 4-diameter magnification (Eder-Hufford esophagoscope) with the transesophagoscopic ruler, previously described[3]. In spite of the definitiveness of the measuring techniques, it is necessary to simplify classification in order to avoid false precision. Endoscopically, varices demonstrate many variabilities: differing conditions are found in different segments of each esophagus, varix diameter is uneven, veins of different sizes occur side by side, and the degree of relaxation of the patient to some extent governs varix diameter.

Classification of varix severity has arbitrarily been established as follows:

a) EXTENT: measurements of extent of involvement are converted to 1/6, 1/4, 1/3, 1/2, 2/3, 3/4 and 100% of the organ length.

b) DIAMETER: severe (in the esophageal segment most severely involved, most of the varices measure six or more millimeters in diameter), moderate (3 to 6 mm.), and mild (less than 3 mm.).

The clinical features studied were, with varying degrees of comparative significance from patient to patient, changes in hepatomegaly, splenomegaly, and ascites. It is to be emphasized that there are many factors other than portal venous pressure controlling these features. Furthermore, variation in one is not necessarily accompanied by similar variations in the others. It was found, however, that as the different features changed in relation to each other, no reciprocal patterns were formed. Because, too, none reflects variation in the utilization of a single native portacaval anastomotic channel, all three were judged together in evaluating clinical progress. Prominence of superficial abdominal veins is largely a measure of utilization of a single collateral system, and this finding will not be discussed at this time.

Results. The repeat esophagoscopic examinations revealed that the varices had undergone change in 36 instances (31 patients). In 22 the varices were worse, either in extent of esophageal involvement or variceal diameter or both, and in 14 they were better. Table 1 correlates the nature of the alterations with the interval between successive examinations. A suggestion is found that in most instances more than a few weeks were required for conditions governing varix severity to change.

Correlation between alterations in varix severity and changes in clinical signs is outlined in Table 2. This correlation was notably poor. In some patients the varices became worse in spite of decreased splenomegaly, hepatomegaly and ascites, and in others there was improvement in the face of a worsening clinical situation.

TABLE 1.—CORRELATION BETWEEN SEVERITY OF VARICES AND INTERVAL BETWEEN ESOPHAGOSCOPIC EXAMINATIONS: 75 REPEAT EXAMINATIONS, 60 PATIENTS

Interval, weeks	*Number examinations*	*Number unchanged*	*Number worse*	*Number better*
1-2	23	15	5	3
3-4	10	6	2	2
5-8	18	10	2	6
9-12	7	3	2	2
13-20	4	1	2	1
21-32	6	3	3	
33-50	7	2	5	

The development of varices was observed in 7 patients whose esophagus had previously been free of varices and of prominent submucosal veins. The inter-examination periods had been 2, 2, 2, 17, 23, 65, and 116 weeks. Changes in physical signs had not occurred in 4 cases. There had been increasing ascites in one, decreasing ascites in one, and improvement in both splenomegaly and hepatomegaly in one. The newly developed varices were classed as mild in 5 and moderate in two. One-sixth of the organ had become involved in one, 1/4 in two, 1/2 in three, and 2/3 in one.

Previously observed varices had disappeared spontaneously in 7 patients, and could not be reproduced upon Val-

salva maneuver. Inter-examination intervals had been 1, 2, 3, 6, 7, 8, and 16 weeks. Three patients meanwhile had shown no change upon physical examination. Three showed improvement in all abnormal physical signs, and the last had lost ascitic fluid during an otherwise static course. The varices which disappeared had been classed as moderate in 6 instances and mild in the other. One-quarter of the esophagus had been involved in two, 1/3 in three, and 2/3 in two.

TABLE 2—FINDINGS UPON 75 REPEAT ESOPHAGOSCOPIC EXAMINATIONS: CHANGES IN SEVERITY OF VARICES IN RELATION TO CHANGES IN PHYSICAL FINDINGS

Changes in physical findings	*Number examinations*	*Varices unchanged*	*Varices worse*	*Varices better*
Unchanged	44	28	9	7
Worse	13	4	8	1
Better	18	7	5	6
Totals	75	39	22	14

Comment. Long-term investigation of varices in relation to the whole clinical picture will be necessary before the natural history of varices can be understood. It is important to know the circumstances surrounding the initial need for pressing the gastroesophageal venous connections into use, the fluctuations of volume flow and pressure within varices under conditions of static portal pressure, the influence of changing portal pressure on varix size, and, especially, the correlations between varix size, portal pressure and propensities toward hemorrhage.

Whatever the various relationships, sudden alterations in the severity of esophageal varices must be recognized, if proper use is to be made of surgical decompression techniques. It is clear that the clinician cannot rely on physical signs to help in evaluating varix severity, nor can he predict fluctuations by these indirect examination methods. The corollary is that no sense of security can be drawn from an improving clinical situation, as far as the varices are concerned.

Spontaneous variceal variation cannot be explained at this time. Varices are viewed as passive shunting systems, and histologic study of the varix wall does not show enough muscular tissue to account for significant contractility. Variations in volume flow and hydrostatic pressure might, then, depend only on the demands of the portal venous volume and alterations in the capacity of the other collateral shunting systems. Neither can be measured at this time. It can merely be suggested that unknown local regulatory mechanisms may from time to time temporarily discourage venous outflow through the other systems, including transhepatic systems, forcing a reciprocal burden on the varices.

Conclusions. As a result of serial esophagoscopic evaluation of varices in 60 cirrhotic patients and comparison with changes in the clinical signs of portal hypertension, it is concluded that there is no constant direct or reciprocal relationship between varix severity and hepatomegaly, splenomegaly and ascites. The state of esophageal varices cannot be estimated from changes in physical findings. Esophageal varices may appear and disappear under the conditions of a static clinical picture.

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THE DEVELOPMENT AND FUNCTION OF A LIVER BIOPSY PROGRAM: TRAINING OF PERSONNEL, DESCRIPTION OF A MODIFIED VIM-SILVERMAN NEEDLE AND CLINICAL VALUE OF 500 BIOPSIES

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Needle liver biopsy was initiated in the European Hepatitis Research Center, part of the 98th General Hospital, in July, 1949, under the auspices of the Armed Forces Epidemiology Board, Commission on Virus and Rickettsial Diseases. At that time two operators were trained by Doctor Gerald Klatskin in a technique employing the Vim-Silverman needle which was used during the remainder of the year with considerable success. In the early months of 1950 the author was also trained in this technique in anticipation of the early departure of the two original operators, which took place shortly thereafter. The program was subsequently developed along lines to be described.

Physician personnel available for training in liver biopsy in the Army at the present time are usually assigned for a limited period only. The majority of such personnel serve in this theater for less than two years as a rule, part of which time is given over to field duty. With the expansion of the liver biopsy program in this hospital, it soon became necessary to train additional operators to carry on; and as these were transferred to the field or Zone of the Interior, still others were trained in the technique. Later, other general hospitals in the command sent doctors to be qualified, and as a result a definite program of training in technique was evolved. We have felt keenly the responsibility inherent in sending out operators who would work without supervision, not only in other military installations, but in civilian institutions when these doctors returned to the civilian practice of medicine. At the outset it was made plain by the theater surgeon that the continuation of the program would depend on strict supervision and the avoidance of complications, within the limits of the procedure. This critical attitude, it is felt, is entirely justified, and has had a healthy effect in carrying on the work.

While any hospital overseas is necessarily out of direct touch with American medicine except for available literature, fresh viewpoints are often obtained from visiting consultants and especially from newly assigned physicians, who come from many parts of the United States. Most of the latter group have had some contact with, or knowledge of needle liver biopsy as practiced in the institution where they were trained, and a number of them have indicated experience which had not been so favorable as ours, or that of others reported in the literature. In some cases they reported curtailment of biopsy because of complications. As a matter of record many types of complications have been reported, and the technique used in all these instances would appear to be of

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the best[3,13,17]. Without any definite basis of fact we can simply say we feel that adherence to certain general principles have kept our complications to a minimum. There have been no major, and few minor reactions in 630 procedures. While recognizing completely that some occurrences may be beyond control, like that of Marshall and his associates who had their first death from hemorrhage on the 655th biopsy[13], we do believe that complications resulting from insufficient training of the operator, disregarding criteria in selection of patients and deviation from the routine of the procedure selected should not occur.

It is not the purpose of this paper to compare variations in technique. From many reports it is obvious that success may be obtained with many types of approach and apparatus. That used at the Hepatitis Center has been the transthoracic biopsy, employing the Vim-Silverman needle. There has apparently been a gradual shift to this approach because of its usefulness in all sizes of livers[4,6,14]; certainly we have found it excellent. In 1950, the author, because of several failures with the unmodified needle, and stimulated by Dr. Voegtlin's description of a needle modification for subcostal approach under peritoneoscopic control[21], made a further modification of his apparatus for use in the transthoracic approach. This has been previously described[15], and a more detailed explanation of its use will be given in this paper.

PATIENT PERSONNEL. The patients biopsied at this hospital were drawn from Service personnel in many parts of Europe. Although most have come from Western Germany, a fair number have been stationed in England, France, Austria, Italy, Trieste, and even Greece and Turkey. By far the greatest number were young adult males making up the Armed Forces in Germany, and by far the greatest number of admissions were on suspicion of hepatitis, all too frequently proven. Within the past two years, however, there have been many referrals for all types of liver disease which could not be diagnosed and treated by ordinary means. Liver biopsy has been the main tool in final disposition and treatment of these cases, and has helped immeasurably in many decisions.

SELECTION AND PREPARATION OF PATIENTS. Patients selected have been on the basis of suspected liver disease; no normal controls have been allowed, which is an obvious precaution in Service personnel. Biopsies have been authorized, however, in follow-up studies of hepatitis patients to determine the eventual outcome and possible residuals following uncomplicated hepatitis. Prothrombin times (Quick method) must be at least 70% of normal, bleeding and clotting times within normal limits. Although some authors have given Vitamin K preparations before and after biopsy[6], we have not followed this practice, since on a few trials it did not appear to alter prothrombin times materially. One pint of blood is typed and cross-matched and held in readiness in the blood bank for each biopsy patient, 50 mg. of Demerol is given approximately one-half hour prior to biopsy, and a syringe containing 0.5 gm. of intravenous Sodium Amytal is kept in readiness during the procedure, in anticipation of procaine reactions. Voluntary participation by the patient is necessary, and he must sign an operative permit of his own free will. We have found little difficulty with refusals, and the undecided patient will usually agree after talking to one or more successfully biopsied individuals who are almost always at hand, on our hepatitis wards. Biopsy may be performed in the patient's room, or

he may be placed in a room near the nurse's office, to facilitate blood pressure and pulse check following operation. We have always performed biopsy on the ward.

Method. The procedure outlined here is given in considerable detail, which may seem superfluous to some. The detailed description is given with two objects: one, for purposes of comparison with that of other operators, who may be interested; two, for its role in training of personnel which appears later. As stated before, no superiority of this procedure over any other is implied, but it should be noted that exact adherence to this set routine is required on our service.

The materials used in performing the biopsy, except for the needle itself, are shown in Fig. 1. They are lettered, insofar as possible, in the order of their use.

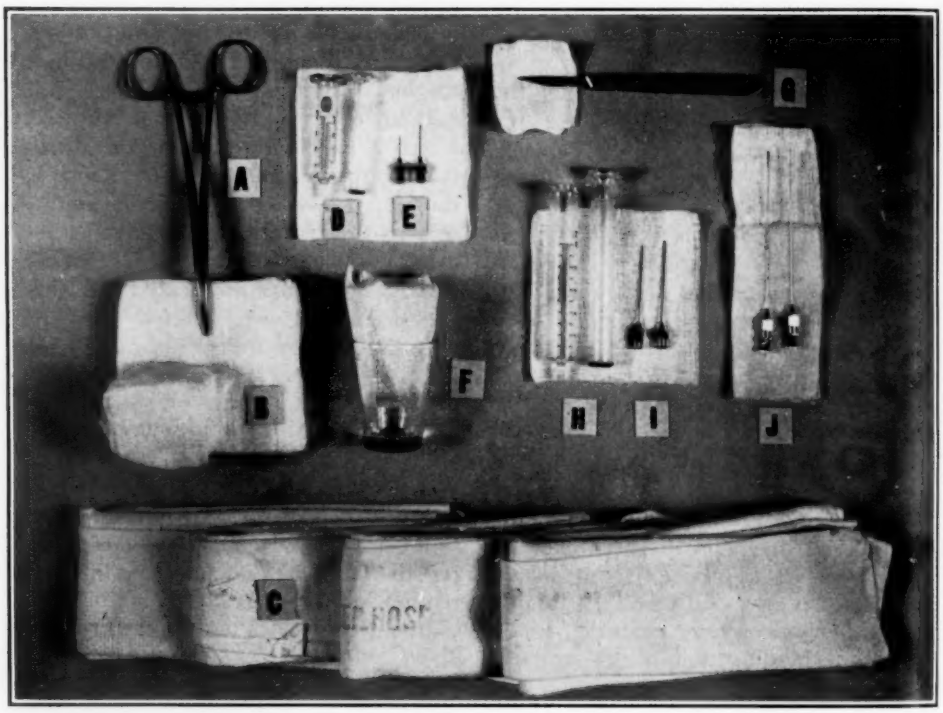

Fig. No. 1.—Biopsy set.

PROCEDURE. *Step No. 1: Marking the patient.* This is best accomplished with a ball point pen, as other types of marking material are liable to wash off during sterilization of the field. The patient is instructed to inhale and then to exhale to the maximum extent, holding his breath at the end of exhalation. An attempt is then made to mark the lower border of his liver, locating it by palpation or percussion. If the liver cannot be located below the costal margin, the margin is marked for possible reference. In the transthoracic approach, exact marking of the lower edge of the liver is not necessary, although a definite attempt to locate it

should be made if possible for purposes of exactness. Failing this, however, marking of the lower rib margin will suffice. Next, the upper border of the liver is determined. The exact outlining of this border is absolutely essential, and it must be located by careful percussion at full expiration. Usually, marks are made on three separate expirations, from front to side, and joined. Rib interspaces are then counted from the clavicle downward approximately to the mid-axillary line. The word "approximately" is used advisedly, since the point of biopsy may not be exactly in this line. Either the eighth or ninth interspace is chosen for the biopsy site, depending on the type of chest encountered. As a general rule, the longer the chest cage, the lower on the lateral chest wall the biopsy site marking is placed. Thus, thick short chests are usually biopsied from the eighth interspace, and long narrow chests in the ninth. The guiding principle is that of avoidance of a possible slice up through the dome of the right lobe of the liver. A misdirected inser-

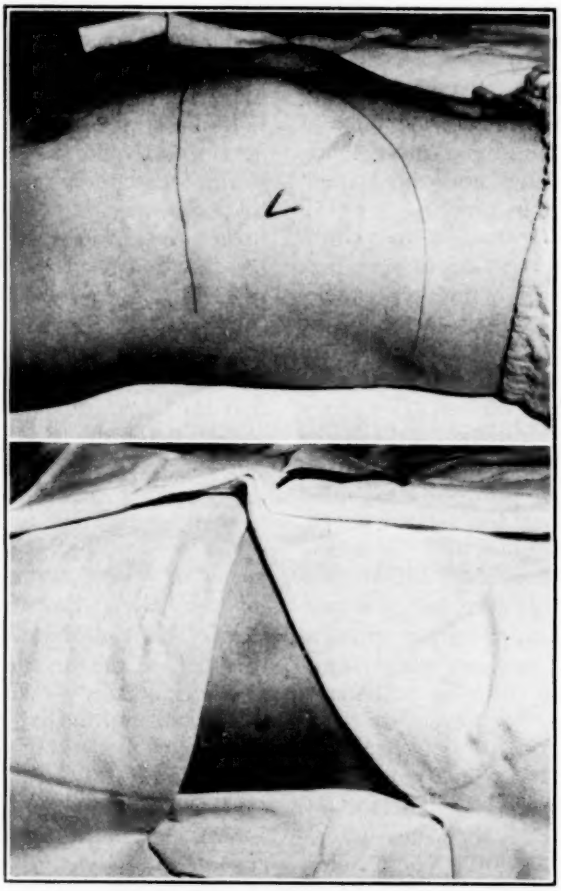

Fig. No. 2.—Details of marking and draping.

tion of the needle in this area might result in 1) a tear of the liver substance, or 2) a non-representative specimen as the entire biopsy may be taken from an area near the capsule. This area is more prone to scarring and may show a picture different from the rest of the liver. The needle must be directed as much as possible for the largest part of the right lobe, and this is best accomplished by locating a spot midway between upper and lower markings[4]. When the desired point is determined, a precise marking is made in the spot selected and the patient cautioned to remain quiet.

Step No. 2. Sterilization and Draping of the field. Sterilization is performed with merthiolate and alcohol (any adequate substitute may be used). A wide area is covered which should include at least the upper and lower liver margins. Materials used are the curved Kelly forceps (A) and the four-by-four gauze sponges (B), the operator having previously donned sterile gloves when the set is opened. Draping is carried out with the sterile towels (C). One is carefully pushed under the patient's body, and it is necessary to warn him to remain quiet at this point. Most patients, unless warned, will roll or rise, disturbing the marking points. The other towels are draped upward across the chest wall, leaving the biopsy site marking in the middle of an inverted V. The forceps may then be used to clamp these towels together over the lower chest anteriorly (Fig. 2).

Step No. 3. Anesthesia and incision of the biopsy site. Using the 2-cc. syringe (D), and the small needles (E) successively, the biopsy site is infiltrated with 1% procaine, which is poured into the medicine glass (F) by an assistant. A small incision is then made with the scalpel (G). The blade should be inserted straight in twice, first with the cutting edge up, then down, to insure easy passage of the biopsy needle.

Step No. 4. Anesthesia of the chest wall, pleura, diaphragm and parietal peritoneum. With the patient breathing naturally, the 10-cc. syringe (H) and smaller of the two needles (I) is used to inject procaine into the intercostal muscles. Several cubic centimeters should be used. Next, the patient is told that for the further anesthesia he must breathe exactly as instructed, in Service parlance, "by the numbers". He is cautioned to breathe in only when told, out when told, and to hold his breath on order. With the longer needle (I) inserted, he is instructed to breathe in and out three times, in a slow cadence. It is essential to watch the patient at this point and make sure that he is following instructions, and that no breathing takes place without order. After the third inhalation and exhalation he is told to "hold your breath, don't breathe or move." The needle is inserted to its full depth, tested to see that it is not in blood vessel or liver, and then procaine is injected along the tract while it is slowly removed. In a few patients with thin chests, the needle may penetrate the liver at this point, and blood will be sucked into the syringe on test. The point must be withdrawn a short distance, and the plunger withdrawn again, until blood no longer is drawn.

Step No. 5. Anesthesia of the liver capsule, and measurement of depth of the liver from the chest wall. One of the special needles (J) is now inserted on the 10-cc. syringe, and the breathing process is gone through as for the longer needle (I). After the third exhalation, the patient is again cautioned not to breathe or move, the spinal needle is inserted until it is felt to enter the liver and approximately 1 cc. injected, the peritoneum and chest

wall being further infiltrated as the needle is withdrawn. The second spinal needle is next inserted into the liver substance with the patient breathing naturally. This is not dangerous with the small caliber needle. Practice will enable most operators to know by feel when the needle enters the liver, but lacking this, movement of the hub of the needle with the breathing, up when the patient inhales and down when he exhales will show that the point is seated in the liver substance. Pulsation of the aorta may also be transmitted. This depth is carefully noted by grasping the needle and laying it on the tray so that the point marked on the needle rests across a small sponge.

Step No. 6. Biopsy with the Vim-Silverman needle as modified by Voegtlin and Nelson. In the 98th General Hospital, a modification of the standard needle has been used since 1950, when it was originally devised. This modification is illustrated in Fig. 3. With the apparatus assembled as shown, the outer needle is adjusted so that it projects beyond the support plate the distance measured on the second spinal needle in step No. 5. In this position the set screw is adjusted so that it is just level with the outer needle hub, and screwed tight on the rigid guide. The needle assembly is now ready for use. The support plate, with the outer needle retracted so that approximately one-half inch projects, is placed firmly

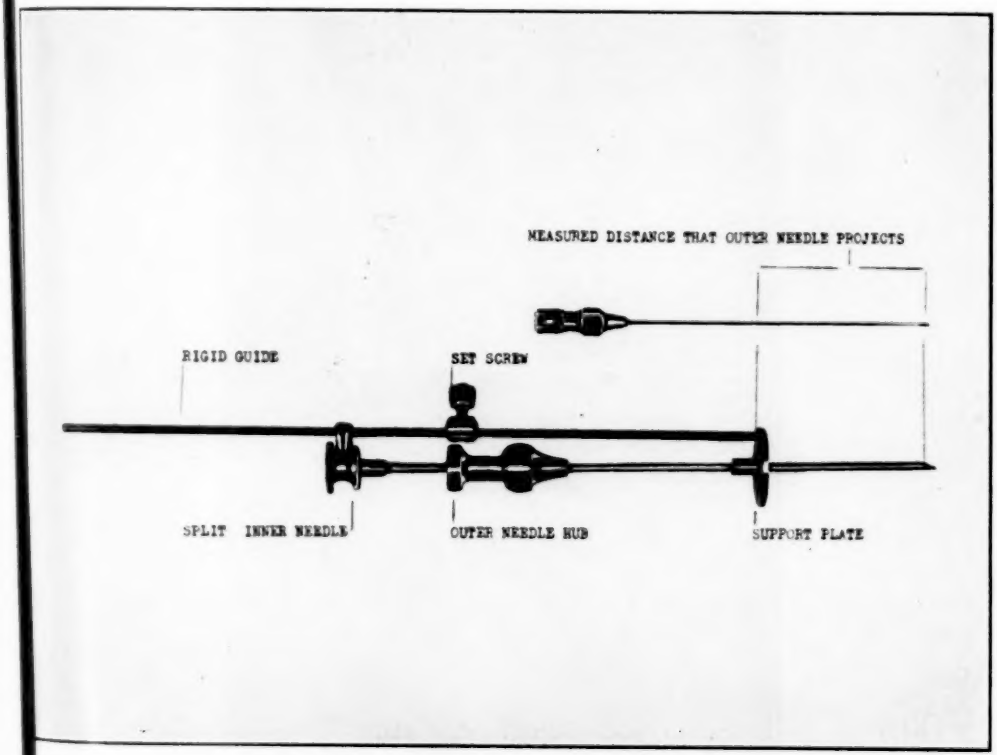

Fig. No. 3.—Modified biopsy needle.

against the skin, and the outer needle seated firmly in the interspace at the biopsy site. The thumb and forefinger of the left hand hold the support plate against the skin, and are kept well away from the needle where it traverses the plate (Fig. 4). (If this precaution is not observed, the glove may catch at this point, halting the needle). Breathing is then carried out as in steps No. 4 and 5, halting the exhalation on the third count. The outer needle is advanced until the hub is level with the set screw, using the right hand (Fig. 5), the inner needle is inserted until it is stopped by the set screw (Fig. 6), the outer needle is again advanced to the support plate with a rotating motion (Fig. 7), and the whole apparatus removed, still with the right hand. (With left-handed operators, position of hands may be reversed with ease).

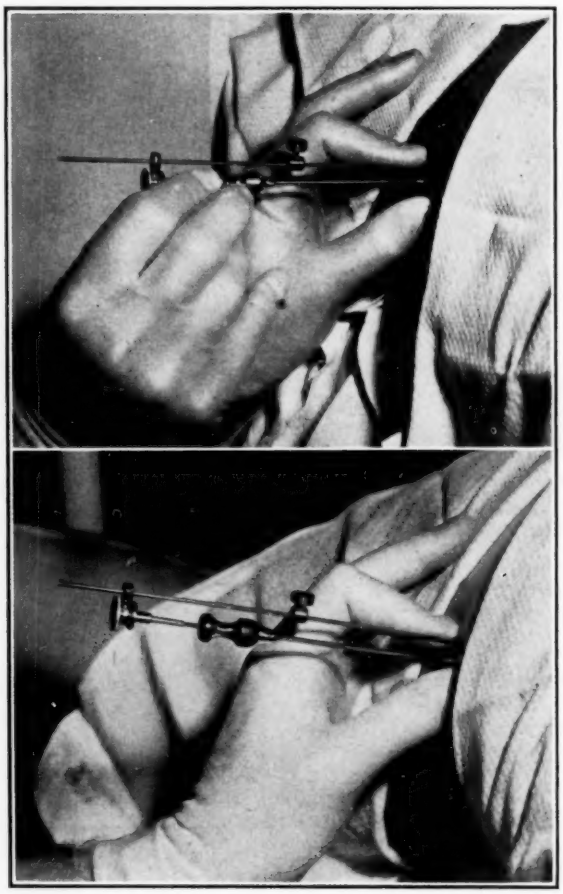

Fig. No. 4.—First position—modified needle in place.

Step No. 7. Removing the biopsy. The inner needle is next carefully removed, and is spread by using the tip of the scalpel passed between the

blades about halfway up the needle. The specimen is removed with the dull edge of the scalpel, after first being immersed in the fixative (we prefer Carnoy's fluid) to make its removal easier. The outer needle should always tilted, and as soon as the biopsy has been removed the bottle should be closed and marked with the name of the patient and time of biopsy. (Too long immersion in Carnoy's solution will ruin the specimen). It is then car-

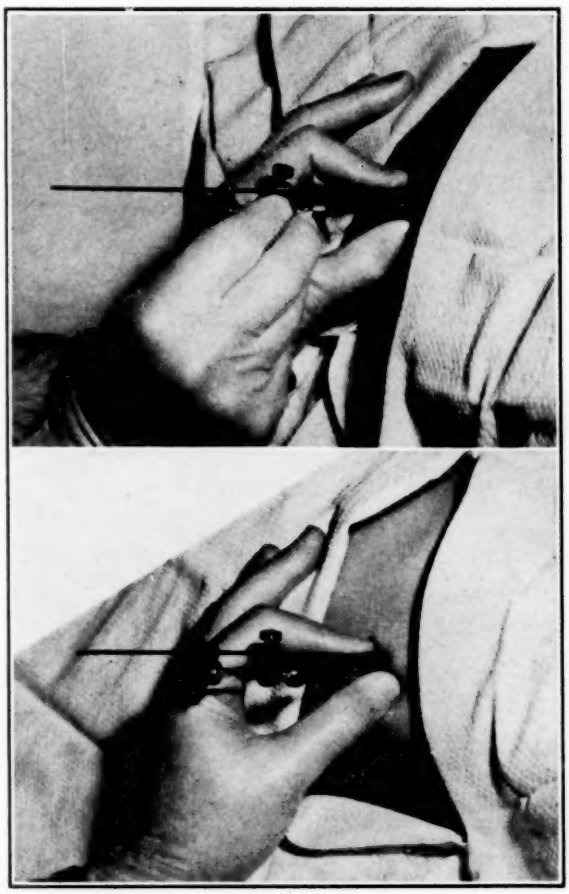

Fig. No. 5.—Second position—outer needle advanced.

be rinsed out with procaine or sterile saline solution, as small parts of the biopsy specimen may break off and remain in the needle, and rinsing at this point facilitates in keeping the needle clean. The specimen bottle during this step is held by an assistant, slightly ried immediately to the laboratory and placed in reliable hands.

Step No. 8. Closing the wound. Alcohol is used to cleanse the wound and area surrounding, collodion is poured directly over the opening, and it is covered by a sterile gauze dressing.

Drapes are removed, and the patient is allowed to move back into the center of the bed, with the pillow under his head. He is instructed that he must not get out of bed, and that he will be checked regularly for 24 hours. (If not so instructed, some patients have a tendency to become nervous with the repeated pulse and blood pressure recordings).

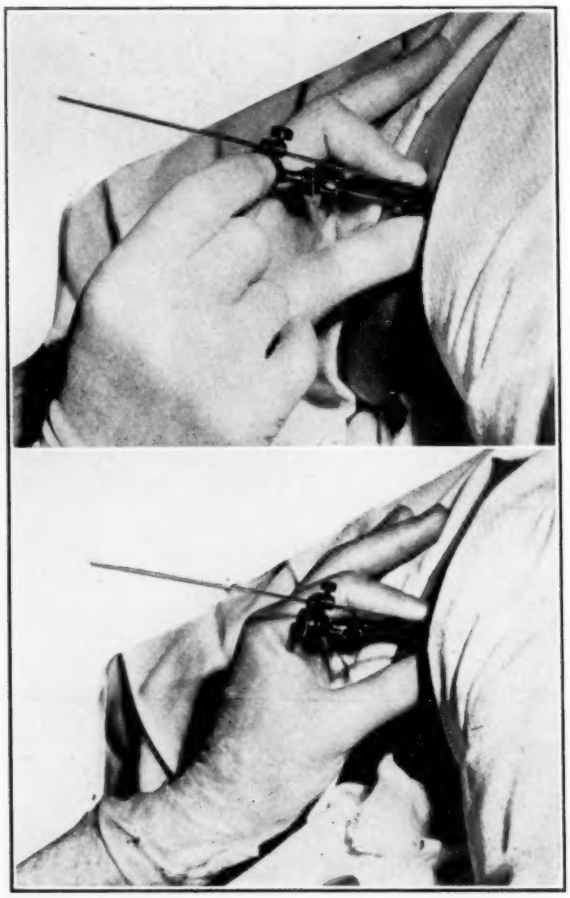

Fig. No. 6.—Third position—inner split needle advanced.

POST-OPERATIVE CARE. The patient is kept in bed for 24 hours following operation, and pulse and blood pressure are checked every half hour. Many variations of this routine have been reported, most of them less stringent[4,6], but we have felt it best to adhere to our original procedure. He is allowed to eat and smoke at regular times, to read, and to have the head of his bed elevated if desired, but impressed with the necessity of remaining down. Some patients become apprehensive, and may need reassurance. After 24 hours he is

allowed up and around the ward; if required he may be discharged from the hospital at this time.

COMPLICATIONS. As noted by others[4,11,14] hemorrhage is the most feared complication. There were symptoms and signs indicating slight to moderate bleeding in three (3) of our patients. These consisted of localized tenderness and slight rigidity in the right upper quadrant, plus some apprehension. Pulse and blood pressure did not show appreciable changes, and no blood was given. These signs and symptoms disappeared within 24 hours. No instance of major hemorrhage has been noted in our series.

Damage to organs traversed by the needle, resulting in bile peritonitis[17], bile thrombosis of pulmonary vessels[3], spread of infection and damage to the right lower lobe of the lung have not been observed, although reported and a definite possibility.

Pain following biopsy has not been a prominent feature, although difficult

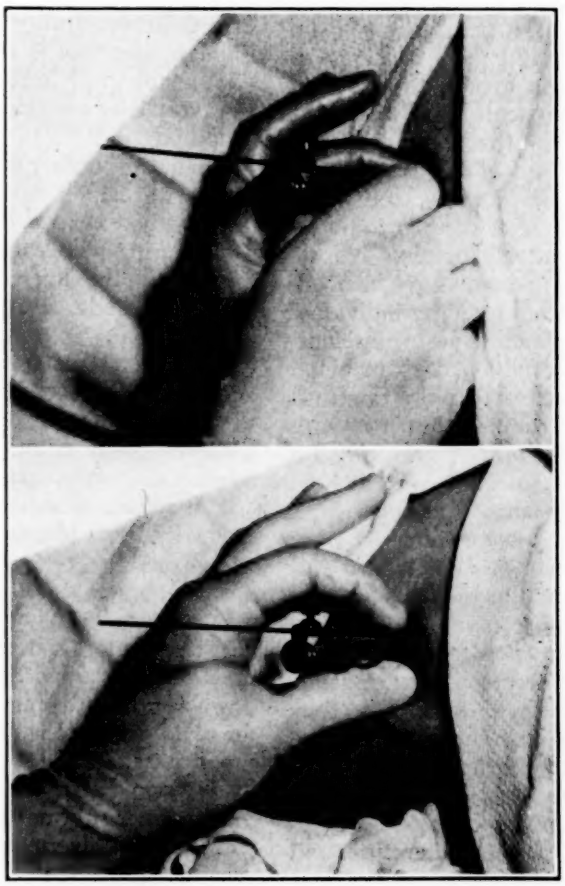

Fig. No. 7.—Fourth position—final advance of outer needle.

to evaluate at times. The occasional excitable patient who complains must be carefully questioned and examined. A few of these will be found to have authentic complaints, but the majority may be handled with reassurance. One of our cases, who caused considerable anxiety among the staff because of severe midepigastric pain, showed no rigidity of the abdomen or signs of bleeding. He was eventually found to be suffering from acute duodenal ulcer, which had taken that period for an exacerbation. We feel the use of fairly large amounts of procaine, and injection beneath the liver capsule to be essential to a relatively painless biopsy.

Two procaine reactions have been encountered. In each case the individual became cold, clammy, lost consciousness and had a sudden drop in blood pressure with increased pulse rate during injection of the anesthesia. Prompt measures in the form of elevating his feet plus the injection of Sodium Amytal, held in readiness in the syringe, brought about a quick reversal of signs and symptoms. In one of these, it was felt that some of the procaine was injected into a vein; in the other, only definite sensitivity could be implied. In a recent case where a history of sensitivity was obtained, and skin tests brought a reaction, a biopsy was done without difficulty by the use of a 1% solution of pontocaine. Little evidence that procaine sensitivity impedes biopsies can be found in the literature, and certainly this has been our experience, although preparations for the eventuality must be made.

RESULTS USING THE VIM-SILVERMAN NEEDLE. Since adoption of the modified needle for routine use, failures have been few, actually less than 2%. Despite considerable practice with the standard needle this degree of efficiency was never reached by the author, if adequacy of the specimen is considered as a criterion. Uniformly large biopsies have become the rule, with less distortion of the specimen. The necessity of making several attempts to secure a specimen through the same opening has been reduced to a minimum. Favorable comment has been made on the quality of our biopsies by personnel of the Armed Forces Institute of Pathology[5]. Enough specimen is obtained for routine histological studies and special tests, such as enzyme determinations, if desired.

Especially gratifying has been the ease with which new personnel has been trained in liver biopsy technique. Time during which the large needle is actually in the liver has been cut to 2 to 3 seconds. First attempts have been invariably successful, and one operator had completed 43 biopsies without a failure at the time of his transfer to the United States on completion of his tour. Such experiences cause confidence and early ease of operation.

This needle modification is not commercially available, but was easily accomplished by two mechanics in our hospital brace shop, who have since manufactured a moderately large number for doctors returning to civilian practice. The support plate was turned down from solid brass on a lathe, and the rigid guide (Fig. 3) cut from rustproof wire. The set screw was also made from brass, as was the support for the inner split needle. The standard 3¾ inch Vim-Silverman needle is easily ground down so that it operates smoothly on the apparatus.

TRAINING OF PERSONNEL. Needle liver biopsy has opened new fields in the study of liver disease. Pathologists are free to admit that the study of these specimens, free from postmortem or postoperative change, have revised their ideas on what occurs in the liver in many diseases, and may lead eventually to the establishment of a complete

sequence of changes hitherto only guessed at in many conditions. Classification and clinical correlation of these changes is still going on, and it is in the interest of progress in modern knowledge of liver that specimens be obtained in the widest variety consistent with safety to the patient.

Trained and responsible operators are essential to this program. They may be obtained only by meticulous insistence on detail under a capable supervisor, until they are themselves able to initiate training in their turn. We feel that there is no substitute for a definite program, carefully carried out, to effect this end. Our program, evolved under the necessities enumerated previously in this paper, has so far trained 12 doctors in liver biopsy, meanwhile keeping complications at the level described and obtaining excellent specimens for examination.

TRAINING PROGRAM. *Step No. 1. Familiarity with the procedure.* The prospective operator is required to watch 8 to 10 biopsies, becoming familiar with materials and technique, which is explained by the biopsist.

Step No. 2. Practice with the biopsy needle. Shortly after, or during step No. 1, he is given a biopsy needle with which he becomes familiar, assembling it and performing 2 or 3 insertions on cadavers, using several intercostal spaces, and observing where the needle pierces the liver on each approach.

Step No. 3. Actual marking and anesthesia of patient. The student goes through steps 1 to 5 under **Method** in the actual patient, under strict supervision. He assembles the needle and hands it to the supervisor, who performs the actual biopsy. This step is repeated as often as necessary to overcome his natural nervousness and gain skill, and is continued until the supervisor is satisfied as to his progress. Some students need only 2 or 3 trials, others as many as 6.

Step No. 4. Performance of whole procedure, including use of needle. This comprises all steps listed under **Method**, in other words, the complete biopsy. Supervision is continued until it is obvious that the new operator is sufficiently skillful to proceed on his own. In our hands, this has never been short of 5 complete biopsies, and may be as many as 8. We have never found anyone unable to become proficient in the procedure, provided he expressed a desire to be trained. The opportunity is offered to all doctors on the service, and they may avail themselves of it if they wish, but no attempt is made to force it upon them. All degrees of natural ability have been encountered, and it is the duty of the supervisor to pace the student to a successful conclusion.

VALUE OF BIOPSY. As pointed out by Berk and Shay[2] and others, the histological picture obtained by needle biopsy is only complementary to the total picture of the patient as obtained by history, physical examination and function tests. The attempt to correlate our still relatively crude methods of analysis of the functional capacity of the liver with the histological picture obtained is often difficult if not impossible. When the biopsy is confirmatory of our clinical evaluation it is gratifying, but when the changes are nonspecific, they may actually serve to cast doubt on the diagnosis. The evaluation of a patient's liver status must still be a clinical one since, as has been pointed out, the area of liver biopsied may not be representative. Specimens with minor histological variations may prove to be more significant in the future if it becomes possible to demonstrate specific enzyme systems by special staining methods.

On the other hand, failure to substantiate the clinical impression in a fair proportion of biopsies should not curtail its use, since it has happily been demonstrated that a number of biopsies may surprisingly reveal unequivocal evidence of disease only suspected by clinical means. In diffuse disease processes, liver biopsy should establish the natural evolution of the pathological process through all stages, if it is only used widely enough by many observers, and the findings classified on a uniform basis. Prognosis and treatment, as well as diagnosis are often profoundly affected by histological examination, and we submit that liver biopsy, while complementary, has become an essential part of any complete evaluation of liver disease.

TABLE 1.—SUMMARY OF FINDINGS IN 501 LIVER BIOPSIES BETWEEN JULY, 1949, AND DECEMBER, 1952

ACUTE VIRAL HEPATITIS

Total Biopsied	*Fatty Metamorphosis*	*Post-Necrotic Scarring*	*Post-Necrotic Collapse*	*Portal Fibrosis*	*Persistent*	*Total Cases Seen*
286	7	23	6	6	11	2311

Per Cent of Biopsies Showing Complications: 18.5
Per Cent of Hepatitis Cases Seen (2311) Showing Proven Complications: 2.3

UNDETERMINED

Total	*Minimal Hist. Changes*	*Fatty Metamorphosis*	*Granulomatous Hepatitis*	*Cirrhosis*	*Portal Fibrosis*	*Others**
215	91	67	19	16	17	5
Per cent of total	42.3	31.2	8.8	7.5	7.9	2.3

* 2 With Abnormal Pigment: 1 Each of Obstructive Jaundice, Amyloidosis, and Pericholangitis.

Our biopsies have been classified according to criteria established by the Armed Forces Institute of Pathology, which has received slides in all cases and given the final evaluation[18]. This system is conservative in that it does not attempt to "read in" diagnoses, but reports the pathology as seen, and states what condition, if any, is compatible with the findings. This paper does not attempt to give specific data in certain diseases, but is more concerned with showing the general usefulness of biopsy and the development of the program at this institution. Due to the mission and function of the Hepatitis Research Center, the procedure has been valuable to us in two main groups of cases: 1) infectious hepatitis, and 2) cases of undetermined etiology. These latter comprise recurrent jaundice of such a nature that the diagnosis is in doubt, hepatomegaly alone or in conjunction with other suggestive evidence of liver disease, and abnormal liver function tests alone or associated with symptoms or any of the foregoing. Serial biopsies have been used little, due to the fact that most cases with chronic liver disease are evacuated to the United States as unfit to remain on field duty. In such cases, our specimens are always available at the Armed Forces Institute of Pathology for future reference by others. Certain types of disease have been the subject of specific survey by our group, and have been reported upon[7,8,9,16].

VIRAL HEPATITIS. Total biopsies in this group during the years 1949 to 1952 were 286. These were performed for two purposes: 1) In 196, to determine the histological status of the liver in cases of delayed healing evidenced by

abnormal function tests, hepatomegaly or continued symptoms, or combination of these: 2) In 90, used in the determination of residuals following uncomplicated hepatitis and in evaluating attempts at treatment with certain agents[7,8,9]. Pathological alterations severe enough to be considered in the disposition of the patient were noted in 53 (18.5%) of the total cases biopsied. The different complications are shown numerically in Table 1. Since viral hepatitis has such a prolonged course, and since we have had a time limit (120 days) for routine treatment, biopsy has proven invaluable in showing chronic states which would necessitate evacuation to the United States. Most biopsies have been performed near the upper time limit for treatment, and experience has shown that those with postnecrotic scarring of any but a slight degree, with portal fibrosis and infiltrates if marked, or with persistent hepatitis should be sent to the Zone of the Interior for further evaluation. Two of these, one with postnecrotic scarring and one with persistent hepatitis, were evacuated but sent to duty in the United States, returned to Europe and when re-evaluated by us 18 to 24 months later because of symptoms, continued to show approximately the same changes as before. It is questionable whether such patients should be subjected to the stress and strain of field duty again. Only by following these cases for a prolonged period will we be able to draw final conclusions as to their outcome, but certainly the prognosis can not be termed optimistic. The absence of any severe histological alteration in cases of prolonged hepatitis is felt to be of more practical value to the Armed Forces, since in these cases we have been able to retain men in this theater past the standard treatment time with good hope of ultimate recovery, and avoid the expense and time loss incurred in an unnecessary trip to the Zone of the Interior. During the period covered by this report (July, 1949, to December, 1952), 2311 patients with clinically proven hepatitis were seen in our Center. Liver biopsies were performed on 286 of these patients, 53 of whom were found to have definite pathological alterations beyond those seen in a typical case of uncomplicated viral hepatitis; for example, we have a rate of 2.3% of histologically proven complications in a group large enough to be considered statistically significant. The proportions of the different types of findings are shown in Table 1. How significant these alterations may be in the future health of the patient can be determined only by prolonged observation and future biopsy over a period of years. It has become increasingly clear to those experienced in the diagnosis and treatment of viral hepatitis that original substantiation of the diagnosis in many cases of recurrent jaundice can be achieved only by biopsy. The evolution of chronic changes in the liver following infection with viral hepatitis will be established only by serial liver biopsy in these proven cases. It is to be hoped that patients will be so followed in the future in many centers, so that an accurate evaluation of the long-term damage done by viral hepatitis may be made.

UNDETERMINED LIVER DISEASE. This group, also shown numerically in Table 1 and comprising 215 biopsies, shows a considerably larger number (57%) of abnormal findings than the hepatitis group. No detailed correlation of clinical and pathological entities will be attempted in this general classification, but it should be noted that 81% of the total abnormal lesions is accounted for by the findings of fatty metamorphosis, portal fibrosis or cirrhosis. The majority of these changes were noted in the livers of patients with a fairly long history of heavy use of alcohol and relatively

poor dietary intake. The biopsy findings in those with fatty metamorphosis alone, the largest group, enabled us to treat and return them to duty with a thorough explanation of their trouble; on the other hand, clear-cut portal fibrosis of any marked degree or cirrhosis necessitated return to the States for further treatment and disposition. The large number of cases with granulomatous hepatitis has been especially interesting. Twelve of these were associated with clinical evidence of sarcoidosis[16], but the remainder with nonspecific signs and symptoms. Two cases showing histologically a peculiar intracellular unidentified pigment, had recurrent jaundice and vague upper abdominal distress. The low incidence of obstructive jaundice (1 case) is rather characteristic of the male age group encountered in service personnel. The single case of amyloidosis was found in a German National biopsied at the request of a member of the University of Munich staff, and had been diagnosed clinically.

It is in this undetermined group that our biopsy program has shown its greatest change with limited use of the procedure in the years 1949 and 1950, and gradual expansion to widespread employment in all types of clinical liver involvement during the 1951, 1952 period. There has been an increasing appreciation of the value of biopsy and confidence in its use during these periods, which may be attained by careful assessments of results and training of personnel.

Summary. 1. A method of needle biopsy of the liver using the transthoracic approach and a modified Vim-Silverman needle is described, together with its employment in the training of personnel in liver biopsy.

2. The value of this procedure in 500 biopsies over a three and one-half year period is discussed, during its employment in the European Hepatitis Research Center.

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DIETARY EGGS AND RHEUMATIC FEVER

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An impressive body of evidence has accumulated indicating that the cause of rheumatic fever is the group A beta hemolytic streptococcus. There is also reason to believe that the disease is produced by a tissue sensitivity reaction involving a bacterial fraction or product rather than by actual bacterial invasion of the affected sites. On this basis, the next step in clarifying the pathogenesis of rheumatic fever is to determine which is the responsible streptococcal fraction or product.

In an investigation[10] of this problem, attention has been focused on one of the two hemolysins produced by the group A hemolytic streptococcus, namely streptolysin S[9], not to be confused with the more familiar streptolysin O. The serum of any individual, sick or well, contains a substance which inhibits the hemolytic activity of streptolysin S. This is a physico-chemical rather than an antibody inhibition. The strength of the serum inhibitor of streptolysin S varies rather widely between different normal individuals. Its activity is dependent in part on serum phospholipid[8], which also varies widely among normal individuals.

One of the ingredients of serum phospholipid is choline, a substance which the human body can neither synthesize nor store in significant amounts[5,7]. It has, therefore, sometimes been classed with the vitamins. The human choline requirement has not been measured, but is probably higher in childhood because of the demands of growing tissues of which it is a constituent. By far the richest dietary source of choline is the egg, which provides about half the quantity of this substance in the ordinary diet[1].

For these reasons and since rheumatic fever is essentially a disease of childhood, a comparison of the childhood egg intake of subjects with rheumatic heart disease with that of normal individuals was undertaken.

Method. Dietary information was obtained verbally. Realizing that answers may be influenced, consciously or unconsciously, by the manner of questioning, an effort was made to keep the wording and the inflections the same for control subjects as for patients.

The following standard questions were asked: Do you like eggs? Do you average about one a day? Did you get plenty of them in childhood, as nearly as you can remember? Answers to the first question were classified as yes, slight or no. Only an active dislike was listed as no. In about one-sixth of those with an active dislike, eggs cause vomiting. For the other two questions, 4 eggs or less per week were arbitrarily taken as few and above this number as ample. If the answer to the last question was hesitant or at variance with present liking for eggs, it was amplified by asking: Did you like them as a child? and Was your family in a position to provide them? This sometimes brought the response that times were hard and few eggs were available. The answer "probably few" was tabulated as few and "probably ample" as ample. A few persons had no opinion and were classified as ample.

Patients with a well-established clinical diagnosis of rheumatic heart disease were interviewed in the cardiac clinics of the Pennsylvania Hospital and the Children's Hospital of Philadelphia through the courtesy of Drs. Joseph B. Vander Veer and Rachel Ash respectively. All but 15 of these patients were adults or adolescents. In the case of children, when the mother was the informant the

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TABLE 1.—LIKING FOR EGGS AT PRESENT AND EGG INTAKE IN CHILDHOOD AS STATED BY 184 PATIENTS WITH RHEUMATIC HEART DISEASE AND 1380 NORMAL CONTROLS
(Expressed as Percentages of Subgroups According to Sex and Race)

	Male White 50 RHD—443 N						*Female White 83 RHD—464 N*						*All White 133 RHD—907 N*					
	Ample		*Few*		*Total*		*Ample*		*Few*		*Total*		*Ample*		*Few*		*Total*	
	RHD	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*
Like	**48.0**	77.2	**30.0**	8.6	**78.0**	85.8	**44.5**	70.6	**24.0**	8.1	**68.5**	78.7	**45.8**	73.7	**26.3**	8.3	**72.1**	82.0
Slight	**4.0**	7.0	**6.0**	4.7	**10.0**	11.7	**6.0**	8.3	**14.4**	7.1	**20.4**	15.4	**5.2**	7.7	**11.2**	5.9	**16.4**	13.6
Dislike	**4.0**	1.1	**8.0**	1.3	**12.0**	2.4	**2.4**	2.1	**8.4**	3.4	**10.8**	5.5	**2.9**	1.6	**8.2**	2.4	**11.1**	4.0
Total	**56.0**	85.3	**44.0**	14.6	**100.0**	99.9	**52.9**	81.0	**46.8**	18.6	**99.7**	99.6	**53.9**	83.0	**45.7**	16.6	**99.6**	99.6

	Male Colored 21 RHD—131 N						*Female Colored 30 RHD—342 N*						*All Colored 51 RHD—473 N*					
	Ample		*Few*		*Total*		*Ample*		*Few*		*Total*		*Ample*		*Few*		*Total*	
	RHD	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*
Like	**71.3**	75.5	**9.4**	10.6	**80.7**	86.1	**36.6**	72.7	**16.5**	4.9	**53.1**	77.6	**50.8**	73.5	**13.7**	6.5	**64.5**	80.0
Slight	**4.7**	4.5	**14.1**	7.6	**18.8**	12.1	**26.6**	8.9	**6.6**	5.5	**33.2**	14.4	**17.5**	7.9	**9.8**	6.1	**27.3**	14.0
Dislike	**0**	1.4	**0**	0	**0**	1.4	**6.6**	3.1	**6.6**	4.3	**13.2**	7.4	**3.9**	2.7	**3.9**	3.1	**7.8**	5.8
Total	**76.0**	81.4	**23.5**	18.2	**99.5**	99.6	**69.8**	84.7	**29.7**	14.7	**99.5**	99.4	**72.2**	84.1	**27.4**	15.7	**99.6**	99.8

	All Male 71 RHD—574 N						*All Female 113 RHD—806 N*						*Total 184 RHD—1380 N*					
	Ample		*Few*		*Total*		*Ample*		*Few*		*Total*		*Ample*		*Few*		*Total*	
	RHD	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*	*RHD*	*N*
Like	**54.9**	76.8	**23.9**	9.0	**78.8**	85.8	**42.4**	71.5	**22.1**	6.8	**64.5**	78.4	**47.2**	73.7	**22.8**	7.7	**70.0**	81.4
Slight	**4.2**	6.3	**8.4**	5.4	**12.6**	11.7	**11.4**	8.6	**12.3**	6.4	**23.7**	15.1	**8.6**	7.8	**10.8**	6.0	**19.4**	13.8
Dislike	**2.8**	1.2	**5.6**	1.0	**8.4**	2.2	**3.5**	2.6	**7.9**	3.8	**11.4**	6.4	**3.2**	2.0	**7.0**	2.6	**10.2**	4.6
Total	**61.9**	84.3	**37.9**	15.4	**99.8**	99.7	**57.3**	82.7	**42.3**	17.0	**99.6**	99.9	**59.0**	83.5	**40.6**	16.3	**99.6**	99.8

RHD-rheumatic heart disease, values in bold face. N-normal.
Liking for eggs is expressed as like, slight and dislike.
Egg intake in childhood is expressed as ample and few.

answers seemed less reliable because of her suspicion that the quality of her maternal care was being impugned. Normal subjects of similar economic status for controls were found chiefly among ward patients without rheumatic heart disease, hospital personnel, Army selectees and prenatal clinic patients.

Results. The results are presented in Table 1. It is noteworthy that 40.6% of all the cardiac subjects believe they ate few eggs in childhood, against 16.3% of the normal controls, and that 10.2% of the cardiacs expressed an active dislike of eggs at present as compared with 4.6% of the normals. The more frequent dislike of eggs on the part of the female was an unexpected observation. Perhaps this is related to the slightly higher incidence of rheumatic heart disease which has often been noted in this sex.

As a rough index of the severity of heart disease, the adult cardiac patients were classified on the basis of their need for digitalis. Of the 62 who were taking digitalis, 49% ate few eggs in childhood, while of those not on this drug the percentage was 34. Thus a deficient egg intake in childhood may be correlated with the severity as well as the incidence of rheumatic heart disease.

A similar trend was noted when the patients were classified on the basis of number of recurrences of acute rheumatic fever. Of the 33 who gave a history of 3 or more acute episodes, 51% ate few eggs in childhood, as compared with 38% of the others.

Only 6% of those who were questioned in this regard said their like or dislike of eggs had changed since childhood. Of these, one-quarter like eggs now but did not as children. The remainder, in whom the reverse was true, were mostly colored women.

Comment. Previous observers have incriminated a lack of eggs in rheumatic fever in a less specific fashion. Coburn and Moore[2] found that only one of 14 rheumatic children belonging to wealthy families ate a normal diet, while 3 were "feeding problems" and the remainder did not eat eggs. They also observed that eggs were one of the foods usually omitted, either because of the cost or the patient's dislike, by 25 children of a low economic stratum who had recurrent attacks of rheumatic fever. For these reasons and because eggs are rich in many essential factors, Coburn and Moore supplemented the diet of rheumatic children in a convalescent home with extra eggs. While this supplement was continued there were no recurrences of acute rheumatic fever although fresh hemolytic streptococcal respiratory tract infections were numerous. However, the results were not thought significant because rheumatic fever was not severe in the locality during that period.

A deficiency in dietary eggs is evidently not a complete explanation of rheumatic fever susceptibility. The severity of streptococcal infection is probably a major factor in the incidence of the disease. Another factor, discussed elsewhere[10], may be the innate level of serum phospholipid. Still another major influence in rheumatic fever susceptibility may be concerned with individual differences in choline requirement, which is presumably governed not only by the serum level of phospholipid but also by the rate of phospholipid turnover, perhaps chiefly by the latter. Engel[4] has described 2 strains of rats with a marked hereditary difference in choline requirement, one strain requiring twice as much as the other. This observation has been confirmed by Copeland[3]. If similar differences exist in humans, an egg intake sufficient to maintain an average normal serum phospholipid level in a person with a low choline requirement might not be adequate for another per-

son with a high requirement.

It is possible that the amount of eggs eaten is merely a measure of the total protein in the diet. However, there appears to be no way of determining the extent to which this is true of the past dietaries of a large group of people. Other observers[2,6] have presented evidence pointing to a general protein deficiency in the diet of rheumatic children. Perhaps the true significance of the evidence regarding protein is as an indication of the choline content of the diet.

Summary. Because eggs are by far the richest source of the dietary choline necessary for the synthesis of serum phospholipid, which in turn is an active component of the natural serum inhibitor of the streptococcal hemolysin known as streptolysin S, dietary histories with regard to eggs were taken from 184 patients with rheumatic heart disease and 1380 normal persons. Of the cardiac subjects, 10.2% actively disliked eggs and 40.6% believed they ate few eggs in childhood either from dislike or inaccessibility, against corresponding percentages of 4.6 and 16.3 for the control group. A history of few eggs in childhood was given by 49% of the patients with cardiac damage severe enough to require digitalis and by 51% of those who had had three or more acute episodes of rheumatic fever. It is suggested that individual differences not only in choline intake but also in choline requirement may play a part in determining susceptibility to rheumatic fever.

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SERUM PHOSPHOLIPID AND RHEUMATIC FEVER

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It is now widely accepted that rheumatic fever is of streptococcal origin. Evidence that acute rheumatic fever, which is essentially a disease of childhood, occurs shortly after infection by the group A beta hemolytic streptococcus has been summarized by Swift[20]. The rheumatic character of the cardiac lesions of experimental hypersensitivity[15] suggests that rheumatic carditis is due to a reaction between a bacterial component and its corresponding antibody rather than actual bacterial invasion of the heart. However, only a small proportion of hemolytic streptococcal infections is followed by rheumatic fever. It seems likely therefore that the agent which is responsible for rheumatic carditis will prove to be a fraction or product of the group A beta hemolytic streptococcus against which most people have a natural resistance, this resistance being defective in a small proportion of the population, particularly in childhood.

In a study of this problem our attention has been centered on streptolysin S[22], one of the two hemolysins produced by hemolytic streptococci of group A, the other being the more familiar streptolysin O. A substance which is capable of inhibiting the hemolytic action of streptolysin S is normally present in human serum[7]. This inhibition is a physicochemical action rather than an antibody effect[8]. Among normal persons the differences in the ability of serum to inhibit streptolysin S may exceed two-fold. The composition of this serum inhibitor is not completely known, but phospholipid is an active ingredient[18]. There is evidence[19,25] that a very weak serum inhibitor of streptolysin S is apt to be accompanied by a low serum phospholipid, whereas a low serum phospholipid is less constantly accompanied by a weak inhibitor. This suggests that a low serum phospholipid is usually a prerequisite to a very weak serum inhibitor of streptolysin S, although it is not the only factor involved.

The serum phospholipid determinations reported herein were undertaken in the course of exploring the possibility that streptolysin S produces rheumatic fever when its serum inhibitor is very weak due to insufficient serum phospholipid. In this connection it is noteworthy that the average normal serum phospholipid is lower in children than in adults.

Plan of Study. Determinations made during the acute phase of rheumatic fever would lack significance since fever from a variety of causes depresses serum phospholipid[1]. We have therefore taken advantage of the observation of Peters and Man[12] that, barring the effect of fever, serum phospholipid is an individualized metabolic constant in the sense that each person's value tends to remain in the lower, middle or upper zone of the wide normal range. Consequently, if serum phos-

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pholipid is found to be low in an afebrile subject with inactive rheumatic heart disease, it was presumably also low in that subject just prior to the streptococcal infection which caused his rheumatic fever originally.

One of the constituents of phospholipid is choline, a substance which for practical purposes the human body can neither synthesize nor store. The production of serum phospholipid is thus dependent on a supply of choline in the diet. The amount which is needed is not known but the requirement is presumably greater in childhood because of the demands of growing tissues for structural phospholipid. It is therefore possible that an adult with a high serum phospholipid had an unduly low level as a child because of inadequate dietary choline. For these reasons, our subjects were questioned regarding their childhood intake of eggs, which are by far the richest source of choline in the ordinary diet. It was found[24] that whereas a history of eating few eggs in childhood was given by 16.3% of normal control subjects, this percentage was 40.6 in patients with rheumatic heart disease, rising to 49 when the cardiac damage was severe enough to require digitalis and to 51 in those with a history of 2 or more recurrences of acute rheumatic fever. The individual responses to this questioning are utilized in the present report.

Materials and Methods. *Subjects.* Patients with inactive rheumatic heart disease were interviewed in the cardiac clinics of the Pennsylvania Hospital and the Children's Hospital of Philadelphia. Patients were excluded from the study if any of the following conditions were present: fever above 100° F. from any cause within the preceding month, pregnancy or cardiac failure.

Sera from normal adults were provided by Wassermann specimens from blood donors. These subjects were not interviewed aside from routine questioning by blood bank personnel regarding heart disease or recent illness. Control blood samples from children under 13 were secured in the outpatient department of the Children's Hospital of Philadelphia from subjects who were having tuberculin tests or were awaiting tonsillectomy. These were essentially normal children who were afebrile at the time blood was drawn. Sera from a class of high school students, mostly 17 years of age, were available as part of Wassermann samples incidental to a course of venereal disease instruction. Those from the 17-year-old subjects were pooled in groups of 10.

Sera. Since postprandial lipemia was found to have no consistent effect on serum phospholipid, blood was taken without regard to the time of the previous meal. Sera with more than a faint trace of hemolysis were discarded. After the addition of 'Merthiolate' (sodium ethyl-mercuri-thiosalicylate, Lilly) to a final concentration of 1:10,000, the serum was stored at 4° C. and tested before it was 6 weeks old. Within this interval significant changes were not found in lipid phosphorus. Thereafter this value usually declined slowly.

Lipid phosphorus. The method used was that of Youngburg and Youngburg as described by Hawk, Oser and Summerson[6]. In the early part of the program analyses were made in duplicate. After statistical analysis of the differences between duplicate determinations on 115 sera showed a standard error of only $\pm$ 0.247 mg. per 100 cc., the majority of subsequent analyses were single determinations. Inasmuch as phosphorus comprises approximately 4% of the serum phospholipid molecule, serum lipid phosphorus values may be translated to phospholipid by multiplying by 25.

Egg histories. The means by which these were obtained have been described elsewhere[24].

Results. The wide range of normal serum lipid phosphorus and the influence of age are illustrated in Fig. 1. No effect of sex or race was evident. The average for age 3 to 12 is 8.2 mg. per 100 cc. and for age 20 to 39 is 9.7, as indicated by the horizontal bars. It appears that the rise from the juvenile to the adult level occurs after the age of 17. The significance of the curve of age at onset of rheumatic heart disease included in Fig. 1 will be discussed below.

In Fig. 2 is shown the distribution of the serum lipid phosphorus of 178 patients with inactive rheumatic heart disease as compared with the average for normal individuals of the corresponding age groups, represented by the horizontal bars carried over from the preceding figure. For the sake of numerical comparisons, the line of the normal childhood average was arbitrarily extended horizontally beyond the

limit shown in the figure to age 19 and then angulated sharply upward, and the line of the normal adult average was likewise extended horizontally to the right, although in actuality it probably climbs slowly. On this basis, serum lipid phosphorus is below the normal average in approximately two-thirds of all the cardiac subjects. It is apparent that with advancing age there is a gradual increase in the percentage lower in childhood and early adult life than it is in later years.

The patients in Fig. 2 who believe they ate few eggs in childhood are specially designated. Under the age of 35, 82% of the cardiac subjects are below average either in lipid phosphorus or childhood intake of eggs, or both. After age 35, this becomes 75%. For the entire group, it is 80%. The corresponding expected figure for normal

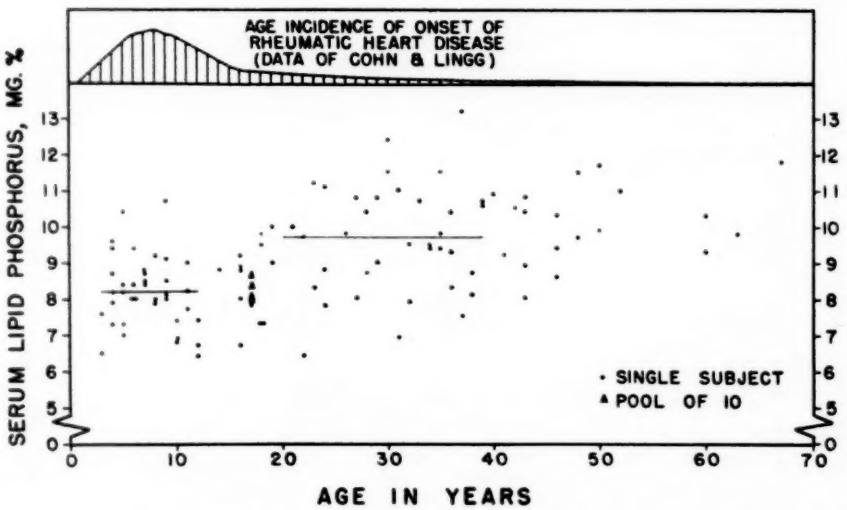

Fig. 1.—Comparison of age incidence of onset of rheumatic heart disease with serum lipid phosphorus of 106 normal subjects plus 4 pools of 10 normal subjects at age 17. Each horizontal bar represents the average of the lipid phosphorus values of all the individuals in the age group it covers. The vertically shaded area, drawn from the data of Cohn and Lingg[2], indicates the incidence of rheumatic heart disease in relation to age.

of readings above the normal average. This trend becomes well established during the fourth decade. Under the age of 35, 71% of the cardiac subjects are below the normal average, whereas after 35 they are about evenly divided above and below. Perhaps this is partly because patients with less severe cardiac damage live longer and partly because of an as yet unknown metabolic peculiarity whereby serum lipid phosphorus in the rheumatic fever-susceptible individual is disproportionately subjects would be 58%, calculated by assuming that 50% would be below average in lipid phosphorus and that of these, 16.3%[24] would have eaten few eggs in childhood.

There were 51 patients who had more than one known attack of acute rheumatic fever, presumably an indication of a high degree of susceptibility. In 46 or approximately 90% of these subjects either the serum lipid phosphorus or the childhood intake of eggs was below average.

There were 58 patients with cardiac damage severe enough to require digitalis. In 82% of these either the serum lipid phosphorus or the childhood intake of eggs was below average. For the 27 patients under age 35 receiving digitalis this percentage was 96.

In Fig. 2 there are 25 patients with serum lipid phosphorus above 10 mg. per 100 cc. and no history of eating few eggs in childhood. These subjects receive particular attention in the table. More than half of them are over 35 years of age. In 5, the onset of rheumatic fever occurred during the worst depression years of 1932 and 1933, when a shortage of dietary eggs was apt to occur for economic reasons. Several of the others had no opinion regarding eggs in childhood and in several the heart disease was slight in degree. This leaves a few with moderate or severe cardiac damage as exceptions for which no explanation is apparent. Rheumatoid arthritis enters the picture as a possible contributing factor in 3 of these, having been certainly present in patient M. A., probably in F. S. and possibly in C. M. Acute rheumatic fever in childhood was questionable in F. S. and definite in the other two. Rheumatoid arthritis is known to be accompanied by an unduly high incidence of heart disease of the rheumatic type and the suggestion has been made[23] that it may produce the same kind of cardiac damage as classical rheumatic fever although different antigens are probably involved.

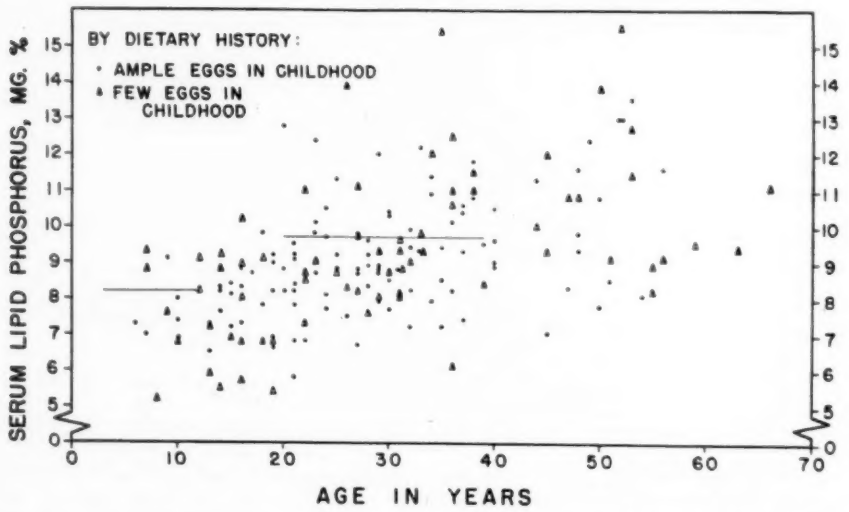

Fig. 2.—Serum lipid phosphorus of 178 patients with inactive rheumatic heart disease in relation to the average values of normal individuals of the same age groups. The horizontal bars representing normal averages are carried over from Fig. 1.

Rheumatoid arthritis may have aggravated the heart disease in these 3 subjects. There was no intimation of rheumatoid arthritis in any other patient of the series.

An increased susceptibility to rheumatic fever has often been noted in the siblings of patients with rheumatic heart disease. The subjects reported herein had a total of 587 siblings among whom there were said to be 29 with rheumatic heart disease, an incidence of 49 per thousand compared with in

expected incidence in the general population of less than 8 per thousand[26]. The 29 rheumatic siblings belonged to 26 members of the series. The dietary and chemical data of these 26 patients did not show significant deviations from those of the rest of the group nor was there a relation between size of family and number of children affected. The familial factor in rheumatic fever may be such a complex mixture of influences, including metabolic, dietary and epidemiologic, that no single factor by itself will be outstanding.

TABLE 1.—INDIVIDUAL DATA ON 25 CARDIAC PATIENTS WITH SERUM LIPID PHOSPHORUS ABOVE 10 MG. PER 100 CC. AND NO HISTORY OF FEW EGGS IN CHILDHOOD

Patient	*LP* mg.	*Age* yr.	*Sex*	*Col*	*Onset* Age yr.	*Onset* Year	*Class**	*Remarks*
F. S.	13.5	53	M	C	?	?	IIIC	Severe chronic arthritis both wrists
J. L.	13.0	52	F	W	23	1924	IIB	Acute rheumatic fever at 10 days postpartum
P. C.	13.0	52	F	W	28	1927	IIIC	
A. L.	12.8	20	M	W	?	?	IB	Likes eggs slightly: probably ample as child
F. I.	12.4	49	F	W	33	1935	IIIC	Asthma
A. C.	12.4	23	F	W	5	1933	IA	
S. D.	12.2	33	M	W	8	1926	IA	
M. G.	12.0	29	M	W	11	1932	IIA	Family felt depression but thinks eggs were ample
L. F.	11.7	38	M	W	6	1919	IIB	
C. M.	11.6	48	F	W	8	1911	IIB	Questionable rheumatoid arthritis 5 months in 1942
L. S.	11.6	56	F	C	?	?	IIC	Heart disease found at 55: ? eggs as child
E. P.	11.4	34	M	W	12	1929	IA	Dislikes eggs but thinks he had ample as child
M. A.	11.3	44	F	W	9	1916	IIIC	Residua of rheumatoid arthritis which began in 1937
N. S.	11.3	25	M	W	7	1933	IIB	No opinion about eggs as child
I. C.	10.9	34	F	W	10	1927	IIB	
M. R.	10.8	50	F	W	?	?	IIIC	Heart disease found at 43
V. B.	10.8	38	M	W	8	1921	IIIC	Diphtheria preceded acute rheumatic fever
M. B.	10.6	40	F	W	?	?	IIB	Eggs probably ample as child
M. C.	10.6	37	F	W	?	?	IIB	Unreliable informant: ? eggs as child
E. M.	10.5	24	M	W	5	1932	IIB	
A. G.	10.4	30	F	W	12	1933	IA	
A. H.	10.4	37	F	C	20	1934	IC	Acute rheumatic fever at 3 months postpartum
D. A.	10.3	30	F	W	7	1928	IIB	
J. D.	10.1	36	M	W	12?	1927?	IIC	No opinion about eggs as child: times were hard
M. F.	10.1	23	F	W	9	1937	IB	

* American Heart Association classification of severity of heart disease.
Unless otherwise stated, all these subjects like eggs.

Discussion. Average normal serum lipid phosphorus values of 9.3[4], 9.2[12] and 9.0[5] mg. per 100 cc. have been recorded for adults and 7.6[21], 7.0[14] and 6.9[10] for children. Most of these were relatively small series of cases. Only one group[12] contained more than 100 subjects and in only one[4] was the method for measurement of lipid phosphorus the same as that used herein. Small size of samples and difference in method can account for the discrepancy between our averages and those previously reported. The physiologic basis

for the lower phospholipid level in childhood is unknown.

The data of Cohn and Lingg[2] on the age of onset of rheumatic heart disease included in Figure 1 were derived from a study of 3129 cases. In that series an "onset" after the age of 25 was determined in most instances by the discovery of valvular disease. It is probable that the majority in this category had an unrecognized episode of acute rheumatic fever in childhood. The curve of the onset of rheumatic heart disease up to the age of 15 is not matched by changes in serum lipid phosphorus during these years but it does run parallel with susceptibility to hemolytic streptococcal infection as measured by the incidence of scarlet fever. Nearly 90% of all cases of scarlet fever occur between the ages of 1 and 15[17], with a peak incidence between 6 and 9, as compared with a peak incidence of measles between 3 and 5[27]. The reasons for these age differences are obscure. Low serum phospholipid may render children eligible for rheumatic fever but the age distribution of this disease within the childhood years appears to be governed by the incidence of streptococcal infection. Initial attacks of acute rheumatic fever are rare after childhood except under unusual epidemiologic conditions, as illustrated by Quinn's[13] series of service men who acquired acute rheumatic fever during the last war because they happened to be exposed to streptococcal strains whose virulence had been enhanced by barracks epidemics. Even under these circumstances an age factor was operating, as shown by the fact that most of those who acquired rheumatic fever were between the ages of 17 and 19.

Previous reports[9,21] of serum phospholipid in rheumatic fever showed no particular trend but they did not take into account the effect of fever. This factor has a double importance since it may cause not only an early depression[1] but also a late elevation of serum lipids. In lobar pneumonia, Steiner and Turner[16] found that serum cholesterol, which usually parallels serum phospholipid, was lowest on the second day to sixth day of the disease, rising with the end of fever to levels above normal where it fluctuated rather widely for 3 to 15 weeks before returning to the individual's normal level. The average maximum postfebrile elevation of serum cholesterol above normal was 82 mg. per 100 cc. During convalescence from a variety of acute febrile diseases, Nishishita[11] found a rise in serum phospholipid, although this was not as constant or as marked as the simultaneous increase in cholesterol.

In order to avoid the depressant effect of fever on serum lipids we have used only ambulatory cardiac patients, excluding any in whom there was a suspicion of activity of the rheumatic process. It seems unlikely that the lipid phosphorus of these subjects was diminished as a result of fever, particularly since we have found that mouth temperature must reach the neighborhood of 101° F. before serum phospholipid is noticeably lowered. In the other direction, protection was sought against postfebrile elevation of phospholipid by eliminating subjects who gave a history of intercurrent fever above 100° F. during the preceding month. Strictly speaking, these effects are probably not the result of fever itself but rather of other changes which accompany fever and convalescence therefrom.

The fact that there are many people who have a low serum phospholipid or who ate few eggs in childhood and have nevertheless escaped rheumatic fever shows that other factors must be involved. One influence affecting the incidence of rheumatic fever is un-

doubtedly the severity of streptococcal infection. Another may be the result of individual differences in choline requirement, as suggested elsewhere[24]. It is worthy of emphasis that the amount of phospholipid in a child's serum depends not only on the serum phospholipid level with which he is endowed but also on his innate choline requirement. These two factors do not necessarily vary directly with each other since the choline requirement may be governed more by the rate of phospholipid turnover than by the serum level. Thus a child might have a low serum phospholipid either because his level was naturally low, regardless of choline intake, or because he had a high choline requirement which was not fulfilled. One would expect supplementary dietary choline to protect against rheumatic fever only in subjects with a high choline requirement. However, this must remain theoretical until individual differences in the human choline requirement are demonstrated, similar to those which have been described[3] in the rat.

Still other factors affecting the incidence of rheumatic fever may become apparent as more is learned about the structure and mode of action of the serum inhibitor of streptolysin S, of which only the broad outlines are discernible at present. The details of its character seem to vary among species and sometimes even among individuals of the same species[8]. In fact, there is apparently more than one component of serum with the power of inhibiting streptolysin S, since S-inhibitor, which is partly protein in nature, is found in different protein fractions of serum[8,18]. The complexity of the situation is further indicated by the fact that such fractions have collectively an inhibitory capacity exceeding that of the original serum, suggesting that some of the fractions capable of combining with streptolysin S were linked with each other in the intact whole serum[8]. However, the basic principle seems well established that inhibition of streptolysin S by serum is accomplished chiefly by a lipoprotein complex in which phospholipid has a role of primary importance.

Summary. In addition to the familiar streptolysin O, beta hemolytic streptococci of group A produce another less well known hemolysin, streptolysin S, whose hemolytic effect is counteracted by a non-antibody inhibitor present to a varying degree in all sera. As a streptococcal product against which humans display different degrees of innate resistance, streptolysin S falls under suspicion of being the cause of rheumatic fever.

The effectiveness of the serum inhibitor of streptolysin S depends in part on phospholipid, which varies widely among different individuals but normally maintains a fairly constant level, whether high or low, in any given individual. Furthermore, the average normal serum phospholipid is lower in childhood, the usual time of onset of rheumatic fever.

We have therefore looked for a relationship between serum phospholipid and susceptibility to rheumatic fever, avoiding the acute phase of the disease because fever from any cause is accompanied by a decrease in serum phospholipid. In a majority of 178 patients with inactive rheumatic heart disease, particularly those under the age of 35, serum phospholipid was found to be below the normal average for the age.

Since the synthesis of phospholipid is dependent on a dietary supply of choline, of which eggs are the richest source, dietary histories were taken from these patients, as reported elsewhere. In 80% either the serum phospholipid or the childhood dietary sup-

ply of eggs, or both, was below average. This percentage was still higher in the patients with multiple attacks of acute rheumatic fever or cardiac damage severe enough to require digitalis, reaching 96 in patients who were on digitalis before the age of 35.

These observations are consistent with the possibility that rheumatic fever is produced when a hemolytic streptococcal infection engenders more streptolysin S than the natural serum inhibitor, as a reflection of serum phospholipid, is able to neutralize.

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THE EFFECT OF SINGLE INTRAVENOUS AND ORAL DOSES OF McN-181 (1,4-BIS(1,4-BENZODIOXAN-2-YLMETHYL)PIPERAZINE) UPON THE BLOOD PRESSURE OF HYPERTENSIVE SUBJECTS

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The present report describes the results of the initial acute trial of 1,4-bis(1,4-benzodioxan-2-ylmethyl)piperazine (McN-181, Dibozane*), a new adrenergic blocking agent, in the treatment of essential hypertension. The study was prompted by laboratory investigations indicating that the compound is one of the most potent and selectively acting drugs of this class, is absorbed in significant amounts from the gastrointestinal tract, and is of relatively low toxicity (see below).

The value of surgical sympathectomy in the treatment of certain types of hypertensive cardiovascular disease has been adequately demonstrated. Following the various procedures that have been employed, there is a statistically significant increase in the period of survival[14]; furthermore, a high percentage of patients shows a sustained fall in blood pressure, improvement in symptoms and regression of the pathological changes characteristic of the disease complex (see [7] for references). The introduction of a potent, long-acting adrenergic blocking agent, Dibenamine[9], prompted inquiries into the possibility of accomplishing the same results by pharmacological means. Dibenamine is too irritating, even in highly diluted solutions, to be given other than by the intravenous route, and consequently, its use in the long-term treatment of hypertension has not been practical. A more recently introduced analogue, SKF 688A or Dibenzyline[13], is sufficiently more potent to be effective when given orally in small doses. It has been reported to lower blood pressure in high[6], low[3] and moderate[1,2,12] percentages of patients with essential hypertension.

McN-181 (1,4-bis(1,4-benzodioxan-2-ylmethyl)piperazine or Dibozane), a

*Trade-mark

recently synthesized compound closely related to piperoxan (Benodaine or 933F), has been found in laboratory investigations to be a highly potent adrenergic blocking agent[10]. In its actions in dogs, it differs from piperoxan chiefly in the relatively low ratio of the dose necessary to prevent the hypertensive effect of occlusion of the common carotid arteries or the response of the nictitating membrane to stimulation of the cervical sympathetic trunk ("sympatholysis") and the dose required to block the actions of injected epinephrine ("adrenolysis"). An intravenous injection of 0.3 mg. per kg. of body weight or the intraduodenal instillation of 0.7 mg. per kg. of body weight in αchloralose-anesthetized dogs was reported to reduce the mean arterial blood pressure by more than 25% and the hypertensive response to carotid occlusion by more than 50%; these effects persisted over 1½ hours after the intraduodenal dose. Actions other than those attributable to adrenergic blockade appeared to be minimal. Chronic administration of the compound to rats and dogs over a period of 6 months indicates that its order of toxicity is low[11].

The object of the present study was to provide the necessary information concerning the potency, side effects and oral absorption of McN-181 in hypertensive patients to serve as a basis for long-term investigations of its therapeutic efficacy. Intravenous infusions of McN-181 were administered twice on separate days to each of 5 hypertensive patients and 4 times to one patient. Oral administration was tested 6 times in 5 patients.

Methods and Material. Studies were conducted on patients with benign, established, essential hypertension. The single exception to this classification was patient J. Ly., who had undergone right nephrectomy, with a diagnosis of chronic pyelonephritis, 7 weeks prior to the first administration of McN-181. Routine Sodium Amytal and piperoxan (or, in one case, Regitine) tests were conducted on all patients[4,5]. Piperoxan produced a rise in systolic pressure in all patients, although in 2 the change was not significant (<10 mm. Hg); in 4, the diastolic pressure rose and in 3 it fell slightly (10 to 12 mm. Hg). Following Sodium Amytal, both systolic and diastolic pressure were reduced in 5 of 8 patients; in the remaining 3, only the systolic pressure fell significantly.

Patients who had been on medical regimens (chiefly hexamethonium) were taken off the drugs at least 5 days prior to the administration of McN-181.

Frequent auscultatory blood pressure readings, pulse rates and electrocardiograms employing standard limb lead 1 were taken during the control period while the patient remained recumbent in a quiet room. When readings appeared to be basal, a needle was introduced into the antecubital vein and infusion of the drug was started. Dilutions containing 1.0 mg. of McN-181 per cc. in 5% glucose were prepared immediately before infusion from a stock solution containing 1% McN-181 and 7% lactic acid. During the infusion, the above observations were repeated at one-minute intervals, and the symptoms and signs were recorded. After the infusion was completed, the patient remained recumbent until the blood pressure had returned approximately to the control level. Readings were then taken with the patient in the sitting position, and, when feasible, while standing. Observations were continued until all apparent effects of the drug had disappeared.

A similar procedure was followed when the drug was administered orally. In the first oral trial, in which 3 patients participated, each patient was given a tablet containing 50.0 mg. McN-181. At the end of an hour, during which time no effects were noted, the dose was doubled; successively doubled doses were given at intervals of one to one and one-half hours until hypotensive or untoward effects were obtained. Eight patients took part in the second oral trial. They were divided into 2 equal groups, one of which received the drug and the other placebo tablets of identical appearance at the same time intervals. The identities of the tablets were unknown to the observers. The doses and the time intervals at which they were given are described under results.

Results. A. INTRAVENOUS ADMINISTRATION. *Effects on Blood Pressure and*

Heart Rate. The results of the intravenous administration of McN-181 are summarized in Table 1. The figures in the columns headed "Average Reduction of Blood Pressure" represent approximations of the average values in the periods during and after infusions when the pressure ranges were distinctly below the lower figures recorded at the ends of the control periods. Differences of less than 10 mm. were not considered significant.

During or after the course of 14 intravenous infusions, ranging in dose from 23 to 94 mg. and in time from 9 to 60 minutes, reductions in blood pressure greater than 30/20 occurred 6 times, between 20/10 and 30/20 twice, and less than 20/10, 6 times.

In 4 patients (N. M., J. La., C. A. and C. M.), the infusion of a given total dose at a relatively slow rate produced a more marked fall in systolic and diastolic pressure during or after the infusion period than did the more rapid administration of the same approximate dose. The heart rate showed a greater tendency to rise during the more rapid infusion. On one occasion (Inf. No. 10) tachycardia was pronounced (160 per min.), and a concomitant rise in pressure to 18/6 above the highest figures recorded during the control period occurred.

TABLE 1.—RESPONSES OF HYPERTENSIVE PATIENTS TO INTRAVENOUS INFUSIONS OF McN-181

Inf. No.	*Patient*	*Dose mg.*	*Period of Adminis. (minutes)*	*Control B.P. Minimum*	*Average Reduction of Blood Pressure (mm. Hg)*			*Side Effects*
					During Inf.	*Post-Inf.*	*Duration*	
1	N. M.	50	38	Ps 186 Pd 114	40 25	40 25	60 min. "	Drowsiness; minimal orthostatic hypotension
2	"	80	49	Ps 164 Pd 110	10 10	— —	— —	Drowsiness; minimal orthostatic hypotension
3	"	40	9	Ps 170 Pd 108	— —	— —	— —	Drowsiness; minimal orthostatic hypotension
4	"	94	88	Ps 170 Pd 100	30 30	14 20	30 min. "	Drowsiness; minimal orthostatic hypotension
5	M. L.	23	32	Ps 190 Pd 110	10 20	14 22	60 min. "	Drowsiness; palpitations
6	"	28	12	Ps 160 Pd 90	— 10	44 14	60 min. "	Palpitations; dyspnea, W.-P.-W. complexes (see text); drowsiness
7	J. La.	68	45	Ps 230 Pd 110	30 14	60 24	30 min. "	Drowsiness
8	"	66	23	Ps 220 Pd 110	— 16	10 10	40 min. 30 min.	Drowsiness
9	C. A.	52	35	Ps 190 Pd 122	30 12	34 22	30 min. 20 min.	Restlessness; drowsiness
10	"	60	20	Ps 202 Pd 130	— —	12 —	60 min. —	Palpitations and tachycardia; rise in Ps during infusion; slight drowsiness
11	C. M.	70	60	Ps 268 Pd 126	60 30	64 20	73 min. "	Vomiting. Drowsiness; slurred speech
12	"	76	20	Ps 230 Pd 108	30 10	20 10	130 min. "	Slurred speech, slight drowsiness
13	J. Ly.	80	24	Ps 174 Pd 104	+30 36	— 30	— 60 min.	Palpitations; weakness; dizziness; drowsiness; slurred speech; nausea; precordial pain
14	"	53	55	Ps 180 Pd 90	+30 —	— —	— —	Drowsiness

One of the remaining 2 patients (M. L.) had an extremely labile blood pressure and heart rate; her pressure was reduced each time to approximately the same degree, but during the rapid infusion the electrocardiogram showed the onset of transient Wolff-Parkinson-White complexes and the infusion was terminated. The other patient (J. Ly.) showed a rise in systolic pressure, a reduction in diastolic pressure and tachycardia during the rapid infusion (Inf. No. 13); when a lower dose was given at a slower rate, the increase in heart rate was less, but both the systolic and diastolic pressures rose (Inf. No. 14).

Effects on Electrocardiogram. With the exception of the development of Wolff-Parkinson-White complexes in patient M. L., electrocardiographic changes were not outstanding. In 4 of the patients, the lead 1 T waves were inverted prior to infusion. In 2 of these (N. M., M. L.) they became diphasic, then upright, during each infusion, and reverted to the control appearance shortly thereafter; in the other 2 patients (C. M., J. Ly.) the inverted T waves become diphasic on one occasion each and remained unchanged during the other. In patient C. A., the T waves were diphasic prior to the slow infusion and remained unchanged; during rapid infusion, they changed from upright but reduced amplitude to normal. The T waves were normal in patient J. La., and underwent no significant change during either infusion. Depressed ST-segments in lead 1 of patients C. A. and C. M. were not modified by the drug.

Side Effects. A side effect which was noted consistently was drowsiness. This varied from a slight feeling of tiredness to actual sleep. It was frequently accompanied by a sense of weakness, especially on sitting or standing shortly after the infusion. Orthostatic hypotension was not marked. Even when significant reduction in the recumbent blood pressure occurred, the further fall induced by assuming an upright position was usually slight and was brief in duration.

Other side effects which occurred during the 14 infusions, at the frequencies indicated, included increase in heart rate >10 (8), dizziness (4), palpitation (3), slurred speech (3), dyspnea (3), nervousness or apprehension (3), coughing (2), a feeling of warmth (2), nausea (2), vomiting (1), precordial pain (1) and singultus (1).

B. ORAL ADMINISTRATION. During the first oral trial, none of the 3 patients showed a significant change in blood pressure following a total dose of 350 mg. of McN-181 (50 plus 100 plus 200 mg.). After an additional 400 mg. (total dose 750 mg., over approximately 3½ hours), one showed a moderate reduction in diastolic, one in systolic and one in both systolic and diastolic pressures (Table 2). No significant reduction in pressure occurred on sitting or standing.

In the second trial, all patients who had not received the drug previously were given a 50 mg. tablet or a placebo tablet after the control period. One, who was receiving McN-181, exhibited electrocardiographic changes indicative of varying degrees of auriculo-ventricular heart block, and was therefore eliminated from the study. The remaining subjects showed no change in blood pressure or other effects within an hour and a half of receiving 500 mg. of the drug or the placebo; the dose was therefore repeated. One patient (H. W.), who had developed a moderate reduction in pressure during the first oral trial, exhibited no significant change during the second and complained only of moderate drowsiness (Table 2). Another (V. J.) de-

veloped a moderate fall which persisted for 3 hours and was accompanied by slight dizziness and palpitation on standing. In the third patient (L. L.), the hypotensive effect was extreme. Forty-two minutes after receiving the second 500 mg. dose, he sat up and complained of not feeling well. He then fell back and developed a transient generalized convulsion, lasting about 5 seconds; immediately thereafter blood pressure readings were not obtainable. As soon as his legs were elevated, a pressure of 120/60 mm. was obtained. He was maintained in shock position for 2 hours; a blood sugar determination on a specimen drawn during this period gave a value of 83 mg. per 100 cc., and electrocardiograms showed no change from the initial tracings. The blood pressure remained at a reduced level for more than 5 hours; during this time, the patient was in a semi-stuporous condition but he could be aroused readily. The following day, the patient was restless, confused and disoriented. He was transferred to the psychiatric service, where the psychosis gradually cleared over a period of 5 days without any residual mental aberration.

No significant fall in systolic or diastolic pressure occurred following administration of the placebo (Table 2).

TABLE 2.—RESPONSES OF HYPERTENSIVE PATIENTS TO ORAL ADMINISTRATION OF McN-181 AND PLACEBO TABLETS

Test No.	*Patient*	*Total Dose mg.*	*Period Over Which Given*	*Control B.P. Minimum*	*Average Range of Fall*		*Side Effects*
					Average Fall	*Duration*	
1	J. Ly.	750	3 hr. 27′	Ps 178 Pd 110	— 10–20	— 65 min.	Sleepiness, headache, palpitation
2	J. La.	750	3 hr. 28′	Ps 160 Pd 90	20 —	64 min.	Slight drowsiness
3	H. W.	750	3 hr. 30′	Ps 164 Pd 118	26 26	96 min. "	Sleepiness, shortness of breath, nausea
4	H. W.	1,000	1 hr. 22′	Ps 160 Pd 110	— —	— —	Sleepiness
5	V. J.	1,050	1 hr. 33′	Ps 200 Pd 130	30 20	182 min. "	Slight dizziness and palpitation standing
6	L. L.	1,000	1 hr. 25	Ps 194 Pd 114	40 40	330 min. "	Drowsiness; syncope on sitting up; convulsions; semi-stupor; mental confusion
1	J. Ly.	Placebo 20 Tablets	1 hr. 20′	Ps 170 Pd 105	— —	— —	Slight headache, drowsiness
2	J. La.	Placebo 20 Tablets	1 hr. 11′	Ps 170 Pd 100	— —	— —	Drowsiness
3	C. M.	Placebo 20 Tablts	1 hr. 14′	Ps 236 Pd 110	— —	— —	No symptoms
4	I. B.	Placebo 20 Tablets	1 hr. 38′	Ps 190 Pd 120	— —	—	Slight headache, sleepiness; sweating

Discussion. Our observations indicate that McN-181 is capable of reducing systolic and diastolic pressures in certain hypertensive subjects when administered either by intravenous infusion or orally. Individual responses were extremely variable by both routes. In addition, certain side effects have been noted which were not apparent in animal experiments[10]. Drowsiness, which occurred consistently during the intravenous infusions regardless of changes in blood pressure,

probably represents a direct depressant effect on the central nervous system. This, as well as most of the other side effects of McN-181, have also been reported following the administration of Dibenzylene[2]. The patients' remaining supine for several hours probably contributed to the development of drowsiness during the oral trials, since it was reported by 3 of the 4 who received the placebo tablets (Table 2). The absence of complaints of nasal stuffiness was unexpected inasmuch as this is one of the most common symptoms which occur during the administration of other adrenergic blocking agents[1]. Likewise, as has been mentioned, orthostatic hypotension was relatively slight in spite of significant reduction in recumbent blood pressure, with the exception of patient L. L.

The increase in heart rate, which occurred frequently during infusions when there was no reduction in pressure, may have been due to a direct action of the drug on the nodal or myocardial tissue or to a central cardioaccelerator action independent of adrenergic blockade. The concomitant rise in systolic pressure, fall in diastolic pressure and tachycardia which occurred in infusion 13 (Table 2) are suggestive of an increase in cardiac output along with a decrease in total peripheral resistance. The predominance of the former effect over the vasodilatation resulting from adrenergic blockade during rapid infusions would explain the smaller hypotensive responses obtained under such circumstances. More direct hemodynamic studies will be required fully to explain these observations.

The doses required to effect a lowering of pressure in most of the hypertensive patients seem quite high in view of the hypotensive potency of McN-181 reported for anesthetized normal dogs. Since the drug has not been tested in normal human subjects, it cannot be said whether this represents a species difference or is related to the pathological condition. As Nickerson[8] has illustrated graphically, the elevated blood pressure in long-established hypertension may be dependent chiefly upon renal and extrarenal humoral factors, with the sympatho-adrenal system playing a relatively minor role. If such is the case, the acute administration of an adrenergic blocking agent could not be expected to effect a major reduction in pressure. It is of interest to note in this connection that patient J. Ly., who had a definite history of renal involvement, exhibited a predominantly hypertensive response to the drug in contrast with the various degrees of reduction in pressure shown by the other patients.

In considering the possible therapeutic efficacy of prolonged pharmacological adrenergic blockade with a drug such as McN-181 in comparison with surgical sympathectomy in cases of essential hypertension, certain differences to be expected with the 2 types of procedure should be emphasized. Adrenergic blocking agents, while potentially capable of effecting extensive interruption of nearly all excitatory sympathetic pathways, presumably do not modify the response to sympathetic vasodilator or cardioaccelerator impulses. The former factor probably constitutes an advantage over surgical procedures, the latter a disadvantage. The side effects and variations in the absorption and patient-response to a drug further complicate attempts to predict its value. Furthermore, tolerance may develop to either the therapeutic or the undesirable actions. "Pharmacological sympathectomy" is not an irreversible procedure, hence its employment in

individual cases may be undertaken with much less reservation than can surgery.

A long-term trial of McN-181 in the treatment of essential hypertension appears to be warranted in view of its potency as an adrenergic blocking agent, its absorbability by the oral route and its lack of gastrointestinal irritation. No other potent drug of this pharmacological class which has been tested clinically to date appears to possess the last-mentioned property. Factors which might modify its efficacy as a hypotensive agent during prolonged administration would include the variability of its absorption, the possibility of the development of tolerance to its therapeutic or side effects, and the stages or types of hypertension of the patients selected.

Summary. 1. McN-181 or Dibozane, an adrenergic blocking agent, was administered by intravenous infusion to 6 hypertensive patients on 14 occasions in doses ranging from 23 to 94 mg., and orally to 5 patients on 6 occasions in doses of 0.75 to 1.05 gm.

2. Moderate reduction in systolic and diastolic pressure (30/20 or greater) occurred during or following intravenous infusion on 6 occasions; slight falls (20/10 to 30/20) occurred twice, no significant changes in pressure (<20/10) 4 times, and a predominantly pressor effect was noted twice in one patient. The hypotensive effect usually persisted 30 to 60 minutes after infusion. Relatively slow infusion of a given dose generally resulted in a greater fall in blood pressure and less increase in heart rate than did more rapid infusion of the same dose in the same patient. The possible basis of the difference is discussed. Side effects noted most frequently were drowsiness, slight to marked increase in heart rate and dizziness.

3. Varying degrees of reduction in blood pressure occurred in 5 of the 6 oral trials, and persisted from one to over 5 hours. The fall was profound in one patient.

4. It is concluded that McN-181 is capable of reducing blood pressure in certain patients with essential hypertension, but that there is considerable individual variation with respect to its absorption and effectiveness. In view of its potency, low toxicity and apparent lack of gastrointestinal irritation, the drug appears worthy of consideration for long-term assessment for the treatment of hypertension.

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HYPERTENSION AND MYOCARDIAL INFARCTION IN THE NEGRO*

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In a previous report[6] it was found that coronary occlusion in the absence of hypertension was rare in the Negro. In 690 necropsies performed on Negroes at the Louisville General Hospital from 1930 through 1938, coronary occlusion was found in 29 cases. There were 20 males and 9 females. All had hypertension except one male. Diabetes was present in 4 of the cases.

The present report is a further study of 54 cases of myocardial infarction in Negroes admitted to the Louisville General Hospital from 1942 to 1953. This hospital is a municipal institution and admits, except in emergency situations, only indigent individuals of both races. The diagnosis was made clinically in 41 patients, of whom 28 were necropsied and only at necropsy in an additional 13 instances. In each non-necropsied case, the diagnosis was confirmed by electrocardiographic data.

Table 1 shows the age and sex distribution of the 54 cases. There were 28 males and 26 females. The age distribution was approximately the same in both sexes.

Table 2 shows the incidence of hypertension in both sexes. Of the 28 males, hypertension was encountered in 23, or 82.2%. One additional patient had diabetes, uncomplicated by hypertension. Of the 26 females, hypertension was a factor in 24, or 92.2%. Seven of the females had diabetes in addition.

If the previous study[6] based only on necropsies is combined with the present study of both clinical and necropsy cases, it is found that 90% of Negroes with myocardial infarction admitted to the Louisville General Hospital have hypertension. Of the males, 87.5% have such a factor.

TABLE 1.—AGE AND SEX DISTRIBUTION OF MYOCARDIAL INFARCTION IN 54 NEGROES

Age	*Male*	*Female*	*Total*
20 to 29	1	0	1
30 to 39	1	1	2
40 to 49	6	5	11
50 to 59	5	7	12
60 to 69	9	7	16
70 to 79	5	6	11
80 plus	1	0	1
Total	28	26	54

TABLE 2.—INCIDENCE OF HYPERTENSION IN MYOCARDIAL INFARCTION IN 54 NEGROES

Sex	*Hypertension*	*% of Total*
Male	23	82.2
Female	24	92.2

There are a few reports in the literature as to the relation of hypertension to coronary artery disease in the Ne-

*This study was aided by the Alvin T. Hert Fund for Research in Cardiovascular Disease.

gro. Shohet *et al.*[4] found that serious coronary heart disease, in the absence of hypertension, was relatively infrequent in the Negro race. Moritz and Beck[3] found that the concomitant occurrence of essential hypertension and coronary occlusion was especially high in Negroes (88%). Wartman and Hellerstein[5] found that 15 of 17 necropsied cases of myocardial infarction in Negroes had hypertension. Billings *et al.*[1] found that 9 of 11 Negro patients with an acute myocardial infarction had hypertension. However, in the study by Yater *et al.*[7] of coronary artery disease in army men 18 to 39 years of age, the clinical and pathological features of the Negroes were similar in every way to the Caucasians. When inducted into the army, the blood pressure was only slightly elevated in 3 of 37 Negroes who survived a coronary artery occlusion.

The incidence of hypertension in white women who have a myocardial infarction is 2 to 3 times more than in white men. It is difficult to explain the high incidence of hypertension which we found in Negro males. It is possible that Negroes with a normal blood pressure who have had a myocardial infarction are not sufficiently ill to be hospitalized or they die suddenly. In an analysis of necropsied cases of coronary sclerosis severe enough to cause death, Clawson[2] found that most of the cases which had been hospitalized had hypertension and that sudden death, before a myocardial infarction could occur, was considerably greater in the cases without hypertension. We were unable to investigate in our cases the serum cholesterol, the Gofman lipoprotein S_f 12-20 or the beta-lipoprotein fraction of the blood.

Summary. In Negroes admitted to the Louisville General Hospital, infarction of the myocardium is infrequent in the absence of hypertension. Eighty-seven and one-half per cent of the males with myocardial infarction have hypertension.

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GITALIN IN THE TREATMENT OF CONGESTIVE HEART FAILURE: A CLINICAL STUDY*

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Successful clinical studies during the past few years have revived interest in the use of gitalin, a water-soluble amorphous mixture of glycosides first isolated from *Digitalis purpurea* by Kraft in 1912. Long regarded by the Germans as a superior digitalis preparation, gitalin was for many years overlooked by clinicians in this country, although its clinical use was investigated during the 1930's by Stroud and associates[7], Baker and Bloom[1], and Levy and Boas[6].

In a recent series of investigations, Batterman and associates[2,3] again established the efficacy of gitalin and concluded that it has a lower therapeutic ratio (or wider margin of safety) than other cardiac glycosides. Thus, they reasoned that gitalin is the digitalis preparation of choice for digitalization and maintenance of patients with congestive heart failure.

Subsequently, Hejtmancik and Herrmann[5], although they did not duplicate the low therapeutic ratio reported by Batterman and co-workers, found that gitalin produced definite improvement in most cases of congestive failure refractory to treatment with other digitalis preparations. These results, they thought, tended to support Batterman's conclusion that gitalin has a wider margin of safety than other digitalis glycosides. Still more recently, Haring and Luisada[4] found that the full digitalizing dose of intravenous gitalin was well tolerated by 16 patients with congestive failure, including 2 patients in whom other glycosides were poorly tolerated. These investigators noted that the digitalizing dose of intravenous gitalin corresponds with the oral digitalizing dose, indicating that the orally administered drug is absorbed relatively completely from the gastrointestinal tract.

Method. The purpose of this study was to appraise further the effectiveness, dosage requirements, clinical toxicity and therapeutic ratio of gitalin** in initial digitalization and maintenance of patients with congestive heart failure.

During a period of 1½ years, 49 patients with cardiac decompensation were studied. The patients in general were an unselected group with more or less severe congestive heart failure of miscellaneous etiology (arteriosclerotic heart disease, hypertensive cardiovascular disease, rheumatic heart disease, and luetic heart disease). The group included 3 cases of arrhythmias.

*This study was in part supported by a grant from the White Laboratories, Inc., Kenilworth, New Jersey.

**The gitalin used in this investigation was supplied under the trade name of Gitaligin by White Laboratories, Inc.

Of the 49 patients, 32 were first seen as acute hospitalized cases, 7 of whom were subsequently followed in the cardiac outpatient clinic. Seventeen patients were observed in the outpatient clinic only. The duration of follow-up observation varied from 1 to 48 weeks. The clinical status of the hospitalized patients was observed at least once daily. Clinic patients were usually seen every 1 to 2 weeks or, when only minimal symptoms were present, every 3 to 4 weeks. Clinical observations embraced body weight, apical rate, respiratory rate, blood pressure, liver size and the presence of rales, peripheral edema, dyspnea and orthopnea. Occasionally, measurements of vital capacity were made. Electrocardiograms were taken periodically.

Results. INITIAL DIGITALIZATION STUDIES. Initial digitalization with the drug was tested in 29 patients. In 16 of these, gitalin was administered after the maximum response to other therapy (mercurial diuretics, low salt diet, rest and sedation) had been shown to be inadequate. The remaining 13 patients received no other medication prior to or during digitalization with gitalin.

For digitalization, 1.0 to 4.0 mg. of gitalin were administered 1 to 3 times a day under clinical observation. Signs and symptoms of cardiac decompensation cleared in the average case after a total dose of 5.9 mg. The individual digitalizing dose ranged from 4.0 to 9.5 mg. The time required for digitalization varied from 1 to 5 days with an average digitalization period of 2.6 days. The average digitalization period for the 13 patients treated without other medication was only 1.6 days, but the average total dose required was 6.0 mg.

One-day digitalization was attempted in 6 cases by giving 3 variable doses of gitalin every 6 hours (usually 2.0 mg. for the first 2 doses and 1 or 2 mg. for the final dose). Five of these patients required 6.0 mg. to accomplish digitalization, and one required 5.0 mg.

In all 29 cases, digitalization was obtained without the development of toxicity. This was true even in one case (not included in the averages reported above) of a patient with severe rheumatic heart disease who required 17 mg. of gitalin over a period of 5 days before adequate digitalization took place. The desirability of being able to administer so large a digitalizing dose without encountering toxic symptoms is obvious.

THERAPEUTIC RATIO DURING INITIAL DIGITALIZATION. The ratio between digitalizing dose and toxic dose, expressed in terms of per cent, reflects the margin of safety of a digitalis preparation. For digitalis leaf, digitoxin and digoxin, this ratio has been reported[3] to be approximately 60% indicating that the average digitalizing dose of each of these glycosides is about two-thirds of the average toxic dose. Under comparable conditions, gitalin has been found[2,3] to have a therapeutic ratio of 37%, the average digitalizing dose approximating only one-third of the average toxic dose.

An effort was made, therefore, to estimate the therapeutic ratio of gitalin in 4 of our patients in whom multiple daily doses of the drug were cautiously continued beyond digitalization and until minimal toxic manifestations appeared. Toxicity appeared as bradycardia in one of the patients and as nausea in the other 3. The digitalizing dose in these patients averaged 5.25 mg. (5.0 to 6.0 mg.). The total dose required to produce earliest signs of toxicity averaged 12.5 mg. (12.0 to 14.0 mg.). Thus, in this small group of patients, the therapeutic ratio of gitalin was 42%, a value that is in agreement with the ratio of 37% reported by Batterman and associates[2,3].

MAINTENANCE STUDIES. Maintenance studies were conducted in 20 patients, among whom there were 39 separate

trials on varying dose levels. An adequate trial was defined as consecutive therapy for 4 or more weeks at a given dosage (0.25 to 2.0 mg. daily) or earlier termination of the therapy if toxicity or inadequate maintenance was demonstrated. The results and duration of these trials are summarized in Tables 1 and 2.

The trial results (Table 1) indicate that approximately 0.5 mg. of gitalin is the daily dose most likely to be both adequate and nontoxic for maintenance of the majority of digitalized patients. Toxic manifestations occur with increasing frequency as the maintenance dose is raised above 0.5 mg. and, on the other hand, a lower maintenance dose seems to be adequate for fewer patients.

TABLE 1

Dose (mg./day)	*Trials*	*Number of Maintenance Trials*		
		Well Maintained	*Poorly Maintained*	*Developed Toxicity*
0.25	5	3	2*	0
0.5	12	10	1	1
1.0	11	8	0	3*
1.5	8	5	0	3
2.0	3	1	0	2**
TOTAL	39	27	3	9

* Includes one trial less than 4 weeks
** Both trials less than 4 weeks

TABLE 2

Dose (mg./day)	*Duration of Maintenance Trials*					
	4 wks.	*6 wks.*	*8 wks.*	*10 wks.*	*12 wks.*	*Over 12 wks.*
0.25	2					2
0.5	4			1	2	5
1.0		3	2		2	3
1.5	2		1	2	1	2
2.0					1	
TOTAL	8	3	3	3	6	12

THERAPEUTIC RATIO DURING MAINTENANCE. The accepted method of estimating the therapeutic ratio of a digitalis preparation in patients for whom the minimal maintenance dose has been established consists of determining the percentage of patients exhibiting toxicity when this minimal therapeutic dose is doubled. Utilizing this method Batterman and co-workers[2,3] observed that toxicity occurred in approximately one-third of patients receiving gitalin, as compared with approximately two-thirds of patients receiving other digitalis preparations.

In 9 of our patients for whom the *minimal* maintenance dose of gitalin was established, this dose was purposely doubled. Toxicity developed in only 2 of these patients (22%), the toxic symptoms appearing within 6 to 12 weeks. In the remaining 7 patients, the minimal maintenance dose was then tripled with consequent development of toxicity in 2 of the 7 patients within 10 to 12 weeks. The other 5 patients did not manifest toxic symp-

toms even after 6 to 24 weeks at dosage levels 3 to 6 times their minimal maintenance requirement. These data, summarized in Table 3, lend considerable weight to the previously reported conclusion of Batterman and associates that gitalin has a wide margin of safety.

TOXICITY DURING MAINTENANCE STUDIES. In addition to the 4 cases in which toxicity developed when the minimal maintenance dose of gitalin was deliberately doubled or tripled, toxic manifestations were noted in 5 other cases. These latter cases of toxicity were observed during our trials of various maintenance dose levels. Toxicity occurred in 2 cases receiving daily doses of 1.0 mg. (after 1 and 6 weeks, respectively); in one case receiving a dose of 1.5 mg. daily (after 9 weeks); and in the 2 remaining cases on a daily dose of 2.0 mg. (after 2 and 3 weeks, respectively). In these 5 cases, the drug was stopped after toxicity appeared and the minimal therapeutic dose was not established.

Toxic symptoms were usually noted as electrocardiographic changes in rhythm (bradycardia, first degree A-V block and extrasystoles), and occurred without subjective symptoms in 6 of the 9 toxicity cases. Mild subjective complaints (anorexia, epigastric distress) were noted in 2 cases and severe subjective complaints (nausea, vomiting, yellow vision) in one case.

Discussion. The results of this study indicate that gitalin is definitely a potent and effective preparation for digitalization and maintenance of patients with cardiac decompensation. The average digitalizing dose among 29 patients was found to be 5.9 mg., which closely corresponds with the average figure (5.7 mg.) reported by Batterman and associates. Effective digitalization of 6 patients with 3 doses of gitalin, administered 6 hours apart shows that this drug is also capable of rapid digitalization (within 24 hours).

Our maintenance studies indicate that the majority of digitalized patients can be adequately maintained with a daily dose of approximately 0.5 mg. All but 2 patients in whom a daily dose of 0.5 mg. was tried were satisfactorily maintained. One of the exceptions was a patient with advanced heart disease whose maintenance had always been precarious. The other exception was a patient who had previously been adequately maintained with 100 mg. of digitalis daily. After 4 weeks of gitalin therapy (0.5 mg. daily) the latter patient experienced recurrence of congestive failure.

In one of 3 cases of arrhythmia, an auricular flutter was definitely converted by gitalin. In the other 2 cases, the patients had such prompt subsidence of symptoms after gitalin therapy was started that it was felt that

TABLE 3

Patient	*Minimal Therapeutic Dose (mg./day)*	*Maximal Trial Dose (mg./day)*	*Toxic Dose (mg./day)*	*Therapeutic Ratio Toxic Dose: Therapeutic Dose*
A	0.5	1.0 (6 wks.)	1.0 (6 wks.)	2:1
B	0.25	0.5 (12 wks.)	0.5 (12 wks.)	2:1
C	0.5	1.5 (12 wks.)	1.5 (12 wks.)	3:1
D	0.5	1.5 (10 wks.)	1.5 (10 wks.)	3:1
E	0.5	1.5 (4 wks.)	—	>3:1
F	0.5	2.0 (13 wks.)	—	>4:1
G	0.5	1.5 (24 wks.)	—	>3:1
H	0.25	1.5 (21 wks.)	—	>6:1
I	0.25	1.0 (6 wks.)	—	>4:1

their remissions may have been spontaneous.

With respect to the therapeutic ratio or "margin of safety" of gitalin, our results in general confirm the reported findings of Batterman and his co-workers. Based on accepted methods of estimating the therapeutic ratio of a digitalis preparation, our observations indicate that the average digitalizing and maintenance doses of gitalin are approximately one-third of the respective toxic doses.

It is noteworthy that *subjective* symptoms of toxicity occurred in only 3 out of 9 patients in whom toxic reactions to gitalin were observed. In the other 6 cases, toxic manifestations were reflected solely by electrocardiographic changes in rhythm. This suggests that patients on gitalin therapy should be vigilantly followed to ascertain arrhythmic signs of toxicity. On the other hand, when toxic manifestations are usually objective rather than subjective, patients are less likely to object to further digitalis therapy.

Summary. (1) Orally administered gitalin was evaluated for initial digitalization and maintenance therapy in 49 cases of more or less severe congestive heart failure of miscellaneous etiology. Digitalization with the drug was tested in 29 patients and 39 maintenance trials at various dose levels were made in 20 patients.

(2) Digitalization was accomplished in all cases without development of toxicity. The total digitalizing dose ranged from 4.0 mg. to 9.5 mg. and averaged 5.9 mg. The average time required for digitalization was 2.6 days.

(3) Studies of individual maintenance requirements of gitalin indicated that approximately 0.5 mg. is the daily dose most likely to be both adequate and nontoxic for the majority of digitalized patients.

(4) With accepted methods of estimating the therapeutic ratio of a digitalis preparation, the average therapeutic dose of gitalin was estimated to be well below the average toxic dose.

(5) In 4 patients, in whom the digitalizing dosage was cautiously continued until toxicity developed, the ratio of the therapeutic dose to the toxic dose was 42%. In a group of 9 patients on maintenance therapy, deliberate doubling of the *minimal* therapeutic dose produced toxicity in 2 (22%); of the remaining 7 patients, 2 developed toxicity when the minimal dose was tripled and 5 did not manifest toxicity when the dose was raised 3 to 6 times above the minimal therapeutic level.

(6) Orally administered gitalin is effective for initial digitalization and maintenance of patients with congestive heart failure, and appears to have a wide margin of clinical safety.

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THE EFFECT OF INJECTED HEPARIN ON THE ELECTROPHORESIS OF THE LIPOPROTEINS IN PATIENTS WITH HYPERCHOLESTEROLEMIA*

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The first observations by Hahn[11] on the effect of injected heparin on the blood lipids, showed a gross clearing of the lipemic serum of dogs, while treatment of such sera *in vitro* by heparin had no effect. Weld[22,23] confirmed this finding and demonstrated a clearing of lipemic blood perfused through the hind legs of animals, and a clustering together of the chylomicrons after heparin injection. Van Eck *et al.*[21] showed that the lactescence of serum was due to a lipid fraction which was easily separated by centrifugation and which contained a high proportion of neutral fat and smaller amounts of cholesterol and phospholipid probably not bound to protein. It was this fraction which decreased in patients treated with heparin and in plasmas treated *in vitro* with heparin provided the red cells were also present. Swank[19] noted both a clumping of the chylomicrons and of the red cells in the sera of lipemic dogs treated with heparin. The effect was noted *in vivo* with small amounts of heparin and *in vitro* with larger amounts.

Anderson and Fawcett[2] showed that serum from an animal recently injected with heparin, had a clearing effect on lipemic serum *in vitro* while heparin itself did not. A surface tension lowering effect of injected heparin was noted although heparin alone did not have this effect *in vitro*. A change in the ultracentrifugal distribution of the lipoproteins was noted by Graham *et al.*[9] in which there was a shift of the lipid from the high S_f classes to the lower classes after treatment with heparin. Anfinsen, Boyle, and Brown[3] believe that the clearing of the serum is the result of a "clearing factor" found in fraction III-1, 2, 3 of the plasma which arises from the interaction of heparin and a tissue factor on the protein fraction IV-1.

If such changes in the physicochemical characteristics of the lipids are occurring under the influence of heparin, then alterations should be noted in the electrophoretic pattern of the lipoproteins. Most of the plasma lipid migrates with the alpha and beta globulins where the alpha globulin contains more phospholipid than cholesterol and the beta globulin contains the reverse[17]. The following studies are designed to show the effect of heparin on the electrophoretic pattern of cholesterol and phospholipid in patients with hyper-

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cholesterolemia, using the technique of paper electrophoresis.

Methods. Serum was obtained from fasting patients before and one hour after the injection of 50 to 100 mg. of heparin intravenously and stored in the frozen state until analysis. Electrophoresis of the serum was carried out on paper by a modification of the methods of Durrum[6], and of Kunkel and Tiselius[13], and Kunkel[12], using 6 strips of Whatman No. 3 paper, 10 × 45 cm., between glass plates. Serum, 2.5 cc., was added to the strips soaked in barbital buffer, pH 8.6, ionic strength 0.1, and the electrophoresis carried out between 2 baths of the same buffer at 8 milliamperes per strip for 20 hours at 4° C. The strips were then removed and dried at room temperature and cut horizontally into smaller strips 1 cm. wide and each strip extracted for 8 hours in 3:1 alcohol-ether at 70° C. The strips were then washed with the solvent and removed from the tubes. The solvent was evaporated from the tubes and the cholesterol determined by a modification of the method of Schoenheimer and Sperry[18], after which the sample was evaporated *in vacuo*, the residue digested with H_2SO_4 and the phospholipid determined in the same tubes according to the method of Fiske and SubbaRow[7]. Since the serum does not distribute itself equally between the 6 strips of paper, it is not valid to remove a single strip for protein analysis; therefore, separate strips were subjected to electrophoresis under identical conditions and the protein determined by the bromphenol blue method[10,13].

Results. Decrease in the total cholesterol as determined on the whole serum was noted after heparin in the pathological cases but an actual increase was noted in the normal. The phospholipid in the whole serum showed less striking changes (Table 1). When the total amount of cholesterol separated on the strips was integrated and the value compared with the total cholesterol obtained from whole serum, most of the cholesterol was found to be in the protein bound fraction before heparin. After heparin the value for cholesterol obtained from the strips increased in the diabetic, the nephrotic, and the cholangitic types of hypercholesterolemia (Figs. 1, 3, and 4) and decreased in the familial hypercholesterolemia and in the normal (Figs. 2 and 5). In 2 instances (Figs. 1 and 3) the choles-

TABLE 1.—SERUM LIPID CONCENTRATIONS, MG. PER CENT

	CHOLESTEROL				PHOSPHOLIPID			
	WHOLE SERUM		PAPER STRIPS		WHOLE SERUM		PAPER STRIPS	
	B	A	B	A	B	A	B	A
1. DIABETES	280	220	275	359	337	334	53	65
2. XANTHOMA TUBEROSA	573	443	397	296	577	452	130	184
3. LIPOID NEPHROSIS	1100	640	590	702	962	936	64	104
4. BILIARY CIRRHOSIS	1394	1149	998	1004	564	520	152	256
5. NORMAL	235	210	199	184	105	105	134	126

B = Before heparin; A = After heparin

terol value obtained from the paper strips actually exceeded the value for cholesterol found on the whole serum. In the pathological cases a much smaller portion of the phospholipid appeared to be bound to the protein while in the normal case the value for phospholipid obtained from the paper strips slightly exceeded the value obtained from the whole serum. The phospholipid as determined from the paper strips increased after heparin in the pathological cases but did not change significantly in the case of the normal.

After heparin there were noted changes in the electrophoretic distribution of the cholesterol and phospho-

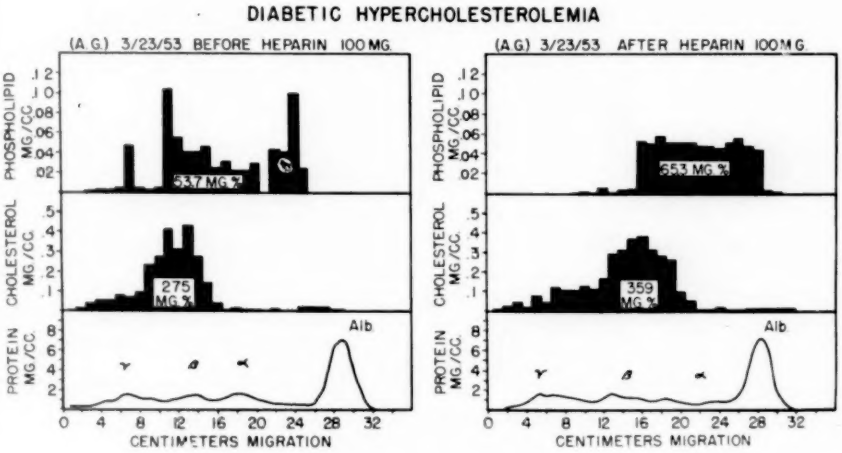

Fig. 1.—Lipoprotein electrophoretic pattern in diabetes.

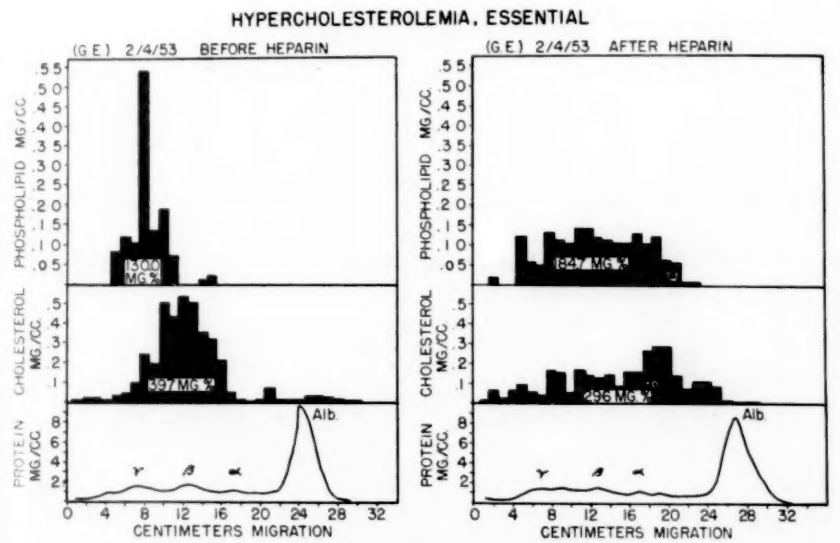

Fig. 2.—Lipoprotein electrophoretic pattern in xanthoma tuberosa.

lipid. Most striking was a tendency for the lipid peaks in the beta globulin region to become blunted and more rounded. In addition to this there was a tendency for more lipid to appear in the alpha globulin region after heparin. Most of the increase which appeared in the integrated values for the cholesterol and phospholipid after heparin in the pathological cases was a

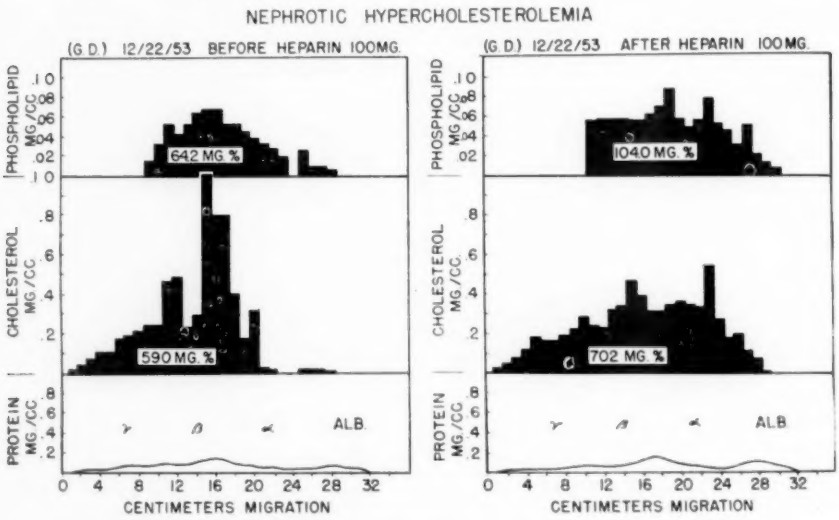

Fig. 3.—Lipoprotein electrophoretic pattern in lipoid nephrosis.

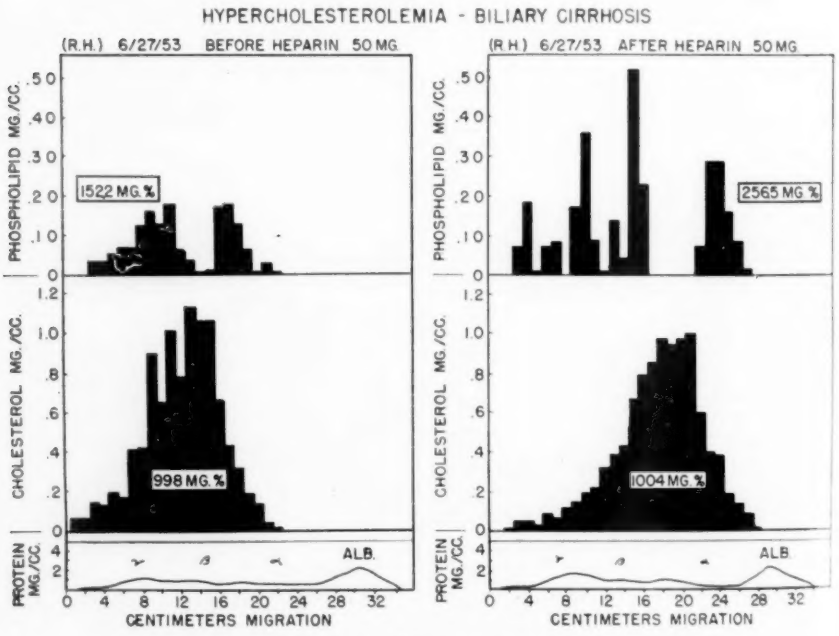

Fig. 4.—Lipoprotein electrophoretic pattern in biliary cirrhosis.

result of the increase in lipids in the alpha globulin region. In each case, including the normal, the peak of the lipid in the beta globulin region showed a shift toward the alpha globulin region. In the case of the biliary cirrhosis (Fig. 4) the phospholipid pattern showed scattering and fragmentation.

No significant change was noted in the protein pattern.

Comment. The decrease in the height of the cholesterol and phospholipid peaks in the region of the beta globulin, occurring after treatment with heparin was associated with a shift of these peaks toward the alpha globulin region. The velocity of migration of a particle in an electric field[1] varies directly with the impressed voltage, the dielectric constant, and the delta potential, and inversely with the viscosity. The delta potential is in turn a function of the particle size and the radius of the assumed Helmholtz layer. An increase in the velocity of migration of some of the lipoprotein particles as seen by the advance of more lipid toward the alpha region, then, could be due to a change in one or more of several factors described above, all of which are a result of a change in the physicochemical state of the lipoprotein complex and consistent with a change in the surface tension properties of the complex as noted by Anderson and Fawcett[2] following the injection of heparin. Another factor, not expressed by the above relationships and peculiar to paper electrophoresis is a possible change in the adhesiveness between the particles and the supporting paper. An increased adhesiveness should theoretically result in a retardation in the migration of the particles, while a decreased adhesiveness should result in more distinct peaks for the lipids, but neither of these 2 combinations of changes were noted, so an important change in the adhesive properties of the complexes could not account *per se* for the observed changes.

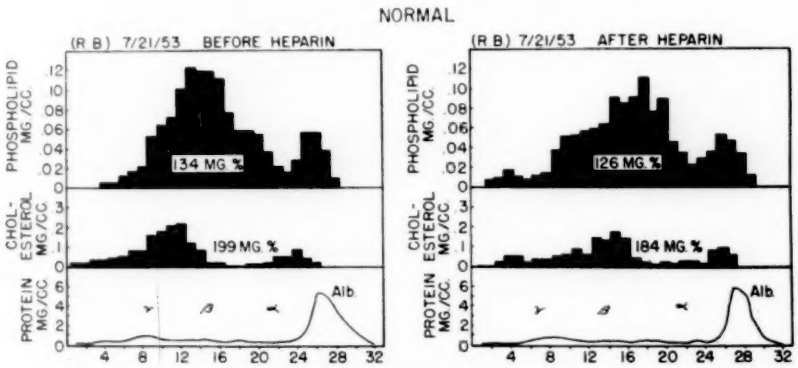

Fig. 5.—Lipoprotein electrophoretic pattern in normal individual.

The solubilities and amphoteric properties of a lipoprotein complex, according to Oncley, Gurd, and Melin[17], are essentially those of the protein moiety, despite the fact that the lipid part may weigh 3 times as much. That the shift toward the alpha region, is a shift in lipid and not of the entire lipoprotein complex is shown by the fact that there is no significant change in the protein electrophoretic curve after heparin. Evidence for the actual ad-

dition of cholesterol and phospholipid to the protein complex after heparin is seen in the increase in the total integrated value of these substances obtained from the paper strips. The mean result appears to be a shift in the lipid peaks in the beta globulin region to a position nearer the alpha globulin region and an increase in the lipid in the alpha globulin region with an increase in the total amount of cholesterol and phospholipid migrating with the protein. Such changes are not striking in the normal. Several possibilities exist as an explanation for this phenomenon, including: 1) the entrance of lipoprotein particles into the circulation from some other "compartment" of the body, thus changing the concentrations of the circulating lipoproteins in the different mobility classes; 2) the entrance of lipid into the protein bound phase from a free phase; 3) the formation of a lipoprotein from which the lipid is more readily extracted with the alcohol-ether.

As to the first possibility, similar changes showing a decrease of the beta lipid peak and an increase in the lipids of the alpha region have been observed to occur *in vitro* by Nikkila[16] when serum from normal individuals was treated with heparin. He noted that the decrease in the area under the beta peak was related to the increase in the area under the alpha peak. The changes were also marked in the neutral fat fraction.

As to the second possibility if a transfer of lipid from the free to the protein bound phase does occur, from whence does the lipid come? The 2 possible sources for this lipid are free lipid in the plasma and the chylomicrons. Evidence that unbound lipid exists in the plasma has been found by Forbes *et al.*[8], who showed by freezing serum and extracting the lipids at 5° C., that a small amount of cholesterol amounting to 12 to 37 mg. per 100 cc. in normals was obtained which was only loosely or not at all bound to protein. The free cholesterol was, however, markedly increased in nephrotics and atherosclerotic rabbits, amounting to 90% of the total serum cholesterol. This unbound lipid might then be a pool from which the protein bound lipid increases after heparin, particularly in the hypercholesterolemic groups.

Weld[22,23] thought that chylomicrons were cleared from the serum after heparin by becoming attached to the red cells. Swank and Wilmot[20] confirmed this work but noted that the chylomicrons frequently disappeared from the plasma under the microscope under the influence of heparin without being visibly attached to the red cells. By exposing plasma to centrifugation such that the chylomicrons were layered on top and the proteins were not layered, they were able to show that injected heparin in the postprandial state in the dog produced disappearance of the chylomicron layer with a concomitant increase in the lipid content of the subnatant clear layer, whereas no increase was noted in the red cell lipid at the same time. The heparin had no effect in the fasting state. They concluded that the heparin had its effect by causing the fat to shift from the chylomicron to an invisible form in solution, presumably the protein bound form.

The increase in the lipid appearing in our electrophoretic studies may then come from either unbound lipid in the plasma or from chylomicrons, and there is no evidence here that the lipoprotein particle is added to the circulation from any other source under the influence of heparin.

The third possibility mentioned above is still to be considered, namely, that the increase in value for the lipids

on the electrophoretic pattern after heparin might be due to lipoprotein complexes from which the lipid is more readily extracted with alcohol-ether. The determination of cholesterol on the unfractionated serum revealed an actual decrease in the value after heparin. The extraction procedure for the total serum cholesterol calls for a short extraction according to the recommendations of Bloor[4] and Boyd[5], while the extraction of lipids from the paper uses a long extraction of 8 hours at 70° C., but extraction of the serum according to the long method in our hands gave only slightly different values from those by the short method although the difference produced by heparin was still present and in the same direction. Man and Gildea[15] had shown that prolonged extraction produced higher values for lipid but Boyd[5] demonstrated that when optimal amounts of ether-alcohol are used that prolonged extraction made little difference in the lipid values. Lever and Mac Lean[14] were able to eliminate the beta anomaly found on schlieren electrophoresis of sera from hypercholesterolemic patients, by cold extraction of the serum with ether. They were unable to lower the beta globulin peak below normal suggesting that the normal lipid was bound in a different way from the abnormal. The other proteins in the whole serum may interfere to some extent with the extraction of the lipids while the extraction from the paper strips is in the presence of much smaller amounts of interfering proteins, thus accounting for the slight inconsistencies in the value of the lipids from the paper strips. It would thus appear that the increase in the lipid values on the electrophoretic strips is a true increase and not simply a result of a change in extractability of the lipids after heparin.

In the cases of hypercholesterolemia described here, the change following heparin seems to be that of a decrease of varying magnitude in the total cholesterol and phospholipid in the serum and an increase in these substances in the protein bound phase, as well as changes in the mobility of the lipoproteins.

Summary and Conclusions. 1. The effect of injected heparin on the electrophoretic pattern of the lipoprotein was studied in 4 patients with hypercholesterolemia and one normal individual, using the method of paper electrophoresis.

2. In the pathological cases the cholesterol and phospholipid values determined on the whole serum fell following the injection of heparin.

3. In 2 of the pathological cases the cholesterol values as obtained by integration of the values from the paper strips decreased and in 2 the values increased while in the case of the phospholipids, the values increased after heparin injection.

4. There was a change in all cases in the electophoretic pattern of the lipids with a blunting of the beta globulin lipid peaks, a shift of the peaks toward the alpha region, and an increase in the alpha globulin lipid peaks.

5. These studies are consistent with the hypothesis that cholesterol and phospholipid enter the protein bound lipid phase from a free lipid phase under the influence of injected heparin.

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CANCER OF THE THYROID

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CARCINOMA of the thyroid gland has within the last several years stimulated considerable interest. The manifestations of malignancy in this organ are unusual in themselves: the occurrence in younger age groups, the compatability of extensive metastases with a protracted course, and the rather common appearance of metastasis as the major or only presenting symptom. The prevalence of thyroid cancer has been re-evaluated, and concepts of surgical prophylaxis thereby changed. Physiologic studies, greatly accelerated and facilitated by radio-iodine, have led to a far more comprehensive understanding of thyroid function, of the relation of the thyroid to other endocrine systems, in particular to the pituitary, and of the development of involutional and neoplastic changes in the cellular structure. The unique possibilities as a therapeutic agent offered by radio-iodine have also instigated a number of pathologic studies clarifying the classification of thyroid cancer in an effort to delineate those categories in which isotopic radiation could be useful.

PREVALENCE. Thyroid cancer is estimated to be about 1% of all cancer. Such data might indicate only that this is not one of the commoner forms of malignant disease; there is, however, one important reason for counting cases. It has been alleged that the number of deaths from thyroid cancer is far less than the incidence reported from surgical material would predict, and the suggestion is made that the

diagnosis of cancer in this organ by the surgical pathologist is not consistent with the clinical incidence, that is, that this is "pathologist's cancer" and not bona fide cancer[79,93]. There can be no question that some of the forms of thyroid malignancy (see below) are indeed histologically equivocal[73], so that in the absence of definite clinical manifestations of malignant potentiality, uncertainty exists after the removal of such lesions as to whether, although they looked like "cancer," they would have acted like "cancer." If it is true, as is proposed, that few individuals actually die of thyroid cancer, then it follows that the diagnosis of surgical material is in error, by including a substantial number of borderline tumors which would never have realized the expectation of dire outcome predicted in the laboratory. An excellent rebuttal to this argument has been provided by Anglem and Bradford, who point out that patients with thyroid cancer do not die in hospitals as a rule, and infrequently in the teaching hospitals from which the necropsy statistics are obtained, so that these statistics cannot accurately reflect the true incidence of deaths. Whereas over a given period there had been no postmortem records of thyroid cancer at Johns Hopkins Hospital, neither had there been necropsies on patients with carcinoma of the oral cavity, a cancer of recognized severity. Over the same period 11 patients with previously diagnosed thyroid cancer are known to have died[1,7]. It is certainly true that where follow-up has been carefully maintained, recurrence, metastases, or death will occur with enough frequency to lend considerable validity to the pathologist's original diagnosis[47,96]. This has often been obscured by the fact that such follow-up must often, for thyroid cancer, extend well beyond the customary 5-year period considered suitable for malignancy at other sites.

It would appear, then, that the incidence of carcinoma in surgical material removed for reasons other than hyperthyroidism, that is, for palpable deformity or nodularity, represents a reasonable estimate of the occurrence of cancer in the nodular goiter in the general population. Reports from a variety of clinics show considerable agreement in a figure of about 5 to 10%, usually closer to the upper limit[14,17,22,50,51,79,85,100]. Support is also afforded by the long-recognized increased incidence of carcinoma of the thyroid in endemic goiter regions, where nodularity is, of course, also much more common[80]. The clinical significance of a frequency of this magnitude is obvious; almost all writers urge removal of nodules for diagnostic and therapeutic purposes.

Thyroid cancer is not in general a disease of older age groups. Quite often cases have appeared before puberty, about one-fifth of all cases before 30 years, and close to one-half before 45 years. Only the anaplastic tumors tend to attack predominantly in the sixth decade, and these types, which are of high degree of malignancy, happily are in the minority. Nodular change is uncommon, even in goiter districts, before 25 years[23], so that the likelihood of such change representing malignancy is substantially higher in young people, about 30%[52]. It is also true that such change will prove to be cancer in the male much more often than in the female[13], although in the absolute incidence females exceed males by a factor of from 2 to 4. Involutional change in the gland, however, has an even higher ratio in the female than this, perhaps 8 to 1; thus the relative frequency of carcinoma in non-toxic nodular glands in the male is in the neighborhood of 15%[85].

PATHOLOGY. The process of dividing a group of tumors into definite categories is bound to be imperfect and subject to a degree of variation or interpretation, especially since the types overlap and may be represented multiply in a single tumor. It is worth noting that a highly undifferentiated tumor on repeated transplant through the guinea pig eye anterior chamber has evolved well differentiated progeny[26], and that a well differentiated, non-malignant adenoma on repeated transplant in mice has developed unquestionable malignant characteristics on continuous stimulation with pituitary thyrotropic hormone[69]. There is no doubt, however, that subgrouping of thyroid cancer has proven profitable in regard to prognostic predictions and therapeutic considerations. The classic study on this subject is that of Graham, 1924[42]. Most pathologists follow in substance the classification of Warren, who proposed three primary divisions: tumors of low degree of malignancy, moderate and high degree[4,62,96].

Malignant Adenoma. These tumors, of low degree of malignancy, are perhaps the most controversial group. They are distinguished from benign adenomas largely by the presence of blood vessel invasion, originally emphasized by Graham[42], which is a criterion not always of unequivocal interpretation. They are thus often follicular and contain colloid, and are separable from the normal gland only by encapsulation, pressure manifestations, and an apparent failure to follow hormonal stimulation so that the cells are in a different secretory phase. It is possible to subdivide these lesions into groups which parallel the embryologic formation of the gland: trabecular, tubular, microfollicular (fetal); this serves little purpose prognostically. Some suggestive cytologic change may be present, and a minimal degree of peripheral invasion, but where especially the latter is marked, such a tumor may better be grouped with the more differentiated adenocarcinomas.

Malignant adenomas gave rise to the concept of "benign metastasizing struma" of the older literature. Bloodborne metastases were found, frequently in the absence of clinical thyroid abnormality, containing what appeared to be perfectly normal thyroid follicles. These tumors are also likely to go undiagnosed at thyroidectomy, and their malignant characteristics become manifest only when distant spread is discovered, which may not occur for many years. In a given group of such tumors, however, the subsequent course will eventually justify the diagnosis of cancer for many of them, and one must assume that this eventuality was forestalled for the remainder by excision of the lesion. In our own group[51], which included a proportion of cases already having metastasized, the 5-year survival rate was less than 60%. Other clinics show a somewhat better prognosis, depending on the stage of the disease when first diagnosed. Prior to clinically obvious metastasis, 5-year survival should be better than 90%, but this figure will drop gradually as the cases are further followed.

Papillary Carcinoma. This lesion is also of low malignancy, as a rule. It is the most common (about 40%) of the various thyroid cancers, and its relative frequency appears to be increasing. Warren had originally distinguished a malignant papillary cystadenoma and a papillary adenocarcinoma, but this is a difficult or impossible distinction to draw, and many pathologists group all predominantly papillary lesions together, as their average age at diagnosis, sex incidence and prognosis are essentially identical[8,67]. Papillary change is quite common in adenocarcinomas, and should not be used

to categorize a lesion as a papillary carcinoma unless it is the major manifestation, with follicle formation definitely subsidiary. The average age for papillary lesions is 45, equivalent to the majority of thyroid cancers, but it composes a majority of the tumors of young people[30,52]. In spite of its benign character, the lesion cannot be considered differentiated by histologic appearance, or in the sense that it can be expected to take up radioactive iodine, with any assurity.

Papillary carcinoma metastasizes early and freely to the cervical lymph nodes, where it may be first discovered as a lateral mass in the neck in young people[24,30]. Such nodes may be replaced entirely by tumor, which, however, characteristically remains for a time confined to the node and invades surrounding structures late in the course of the disease. The "lateral aberrant thyroid" was invoked to explain the presence of these nodes without an evident thyroid primary, since, as Crile writes, the papillary lesions often involve the posterior surface of the gland and grow exceedingly slowly[19]. Although the presence of thyroid tissue in these lateral areas may be an embryologically sound concept, a conclusive demonstration has been repeatedly afforded that the vast majority, or from a practical point of view, all of the papillary carcinomas found in the lateral jugular vein region are in fact metastases from a primary carcinoma of the gland; and that though this primary may be remarkably occult, careful search will almost invariably result in its discovery[3,12,57,59,97]. Extraordinary longevity may occur in these cases[46], which has led to some divergence of opinion regarding the vigorousness of therapy indicated.

Adenocarcinoma. Adenocarcinoma is the tumor of moderate degree of malignancy, and in behavior, prognosis, and appearance corresponds more closely to cancer of other glandular organs of the body. It varies from good follicle formation and colloid production to poor alveolar reproduction without colloid, and, as previously noted, often shows papillary formation. Squamous cell metaplasia may also occur ("epidermoid carcinoma") and with this degree of loss of differentiation the tumor is likely to be more malignant. It is not necessary to hypothecate origin from remnants of other tissue, however. The lesion metastasizes both by lymphatic and vascular channels. Blood vessel invasion may be slower, but does not correlate with prognosis. Five-year survival is in the range of 50%: again, however, late metastatic involvement is not unusual, and 5-year follow-up is clearly too short.

Anaplastic Tumors. Small cell and giant cell tumors comprise the bulk of the tumors of high degree of malignancy; the latter often contain spindle shaped cells. These forms are highly invasive, and commonly not resectable locally. They were diagnosed as sarcomas some years ago, and their epithelial origin may not be obvious. Small-cell tumors are radiosensitive; this is not usually true of the giant cell carcinomas. Prognosis is not hopeless, but it is very poor. These tumors comprise less than 10% of the malignant lesions of the thyroid gland[32,94,96].

Hürthle Cell Tumors. Hürthle cell tumors, characterized by large cells with pale, acidophilic, granular cytoplasm, constitute from 5 to 10% of the thyroid malignancies[10,36]. It is difficult to classify these tumors as regards degree of malignancy, as certain of them behave as malignant adenomas, orderly in structure and metastasizing by the blood stream[87]; whereas others are more comparable to adenocarcinomas, recurring locally and metastasizing to

the nodes in the neck[36]. Hürthle cells are not unique to neoplasms, and are frequently found in involutional nodules. There is no evidence that the cell itself has malignant propensity, and since such cells do not take up radioactive iodine, it would appear that they might well be regarded as an exhausted form, and their tumors be graded according to the appearance of other characteristics of malignancy. Local recurrence of the tumor is common[36], with spread to the cervical nodes, particularly in the less well differentiated forms.

METASTASES. Our own cases[51] are representative of many series of thyroid cancer[94], in that metastases occurred in over a third of the patients and even more commonly in the patients of 20 years or less[21]. (To some extent, cases with metastases will be overweighted in large centers with experience in handling thyroid cancer.) As previously noted, papillary carcinoma has a predilection for the lateral cervical nodes, adenoma malignum for blood-borne metastasis, and adenocarcinoma for both routes. Lymph channels lead also to the Delphian node[14] lying above the gland in the midline, and along the inferior veins into the mediastinum. Involvement of the posterior triangle and the axilla has been noted[21]. Blood-borne metastases go by preference to bone, and only to a slightly lesser extent to the lung.

Bone metastases arise in the medullary canal, are osteolytic, expansile, and frequently pulsatile. The spine, skull, pelvis, ribs, and long bones are favored, roughly in that order[70,86]. The liver is less commonly involved. In the lung solitary metastases are the exception, especially in children, where diffuse nodulation of the basilar portions is often found[30]. In 28 cases of cancer of the thyroid in children reported from Memorial Hospital in New York, 26 cases showed metastases[30].

THE USE OF FROZEN SECTION DIAGNOSIS. Frozen section diagnosis at the operating table, to influence the course of the surgical procedure, has been of great use in certain types of cancers, especially that of the breast. Its use in thyroid cancer is limited because of the degree of differentiation of many of these tumors. When the material submitted has been obtained outside the gland proper, as from a lymph node, the presence of thyroid tissue, however normal looking, is diagnostic of malignancy, but tissue from within the confines of the gland often presents a difficult problem[53]. Even significant papillary change, though unlikely in benign lesions, is not pathognomonic[85]. The difficulties afforded by the paraffin sections are exaggerated in the quick frozen material, which, though it may produce the desired information, cannot be relied upon to do so.

CLINICAL OBSERVATIONS. *Toxicity.* Carcinoma associated with toxic diffuse goiters is rare but not unknown[31,100]. Several series suggest that the incidence in exophthalmic goiter coming to operation is less than 0.5%[17,72]. Goetsch found minute adenoma formation commonly in conjunction with the hyperplastic changes of diffuse toxic goiter, and presented 9 cases considered malignant[40]. The prognosis, nevertheless, is good. Cattell considers all such cancers to be small, localized, and of low malignant potential[8]. Toxic nodular goiter, on the other hand, is frequently associated with carcinoma; most writers feel that the incidence is not as great as in the non-toxic goiter group, but certainly significantly greater than in the population at large. The malignancy itself is not responsible for the hyperfunction, with almost no exceptions. The actual percentage figures are, of course, dependant on the

criteria for a diagnosis of toxicity, which explains their discrepancy from various clinics. The figure given by Pemberton of 33% toxicity in a large group of thyroid cancer patients[90] is higher than the currently prevailing data would indicate.

Solitary Nodules. When a single mass can be felt in the substance of the gland, there is uniform agreement that the likelihood of such a lesion being malignant is 20% or better[13,15,32,85,100]. It should be realized that the solitary nature of a nodule is a clinical diagnosis, not a pathologic one, as many such glands will prove at gross anatomical examination to contain multiple nodules[32,53]. Nevertheless, this clinical observation is so striking that it would seem mandatory that an isolated nodule be removed. It is surprising to find an occasional dissent[43].

Clinical Signs of Malignancy. Although the usual findings which suggest malignancy may be present, thyroid cancer cannot be expected to present fixation or unusual hardness, with any regularity. Such findings are considerably more typical of thyroiditis. Tenderness and sudden enlargement indicate hemorrhage into a nodule, which may be involutional or neoplastic. An acceleration of growth in a long-standing goiter will usually mean malignant change. Dysphagia and hoarseness are common with any thyroid enlargement; if, however, definite recurrent-nerve paresis is objectively demonstrated, it will be found to have arisen from thyroid cancer in most instances[22]. In spite of the relative benignity of thyroid cancer, one should not wait until the nature of a lesion is unmistakable before recommending treatment, as the prognosis varies inversely with the certainty of clinical diagnosis[95].

TREATMENT. *Surgery.* Surgery remains the major weapon in the control of thyroid cancer. As the disease is more carefully followed, and it becomes apparent that many deaths may be anticipated well beyond the 5-year period, the tendency is definitely toward more radical treatment. The fact that a malignancy is slow-growing is not a justification for treating it conservatively, when there is a reasonable expectation of complete extirpation without undue risk or significant mutilation. The initial step in surgical treatment is excision of the lesion for biopsy, and since *a*) frozen section will often fail to establish the nature of the lesion, and *b*) simple enucleation may be inadequate therapy for even well differentiated tumors, most clinics employ total or nearly total hemithyroidectomy for this purpose. When lymph nodes are clinically involved, this operation should be supplemented by radical neck dissection on the affected side.

After establishment of diagnosis, either immediately or following an interval for paraffin sections, further surgical procedures are not standardized. Most surgeons do not advocate more than an adequate local excision for *adenoma malignum,* because it is unlikely to involve local nodes. Total ablation of the involved lobe and isthmus and ipsilateral node dissection for *adenocarcinoma* and where possible, for the highly malignant tumors irrespective of node involvement, is in conformity with cancer surgery at other sites[58]; it is not, however, always practiced in the absence of node involvement, especially when the tumor is very well differentiated (that is follicular). *Papillary carcinomas* are currently a subject of debate. Crile reports 18 cases treated by initial excision of the lesion, and local excision of involved nodes as they appear, arguing that his cases are all alive, that the tumor in the nodes is confined

and does not infiltrate, and that the majority of his patients are young women whom he hesitates to mutilate by neck dissection[20]. This may prove to be a short-term point of view, not by years but by decades. MacDonald and Kotin[63] allege that bilateral involvement of the gland itself is commoner than usually recognized[94], and that following the principle of control of local disease before node dissection, propose total thyroidectomy. In their opinion, neck dissection should not be performed prophylactically, but only where the nodes are clinically involved, and the routine procedure should consist only of extending the dissection locally to the ipsilateral carotid region with removal of a few nodes in this vicinity. It is difficult to see the advantage of this latter part of the operation, since if the nodes are involved, it is inadequate, and if not, unnecessary. Cattell has found node involvement in 50% of the cases of papillary carcinoma whose necks he has dissected; the number of these not evident clinically is not stated, but he is obviously leaning strongly toward prophylactic dissection[7,8]. Common practice appears to be not to dissect the neck prophylactically in the absence of demonstrable node involvement, but to wait until this is manifest and then do so[15,16,48]. In this sense, the situation is analagous to that of squamous epithelioma of the lip. It is our feeling, however, that in young people, although the prognosis is good, the life expectancy is long, and prophylactic neck dissection should be given serious consideration in this group.

It is also important to note that incomplete removal of an extensive, that is, "inoperable" tumor has many desirable aspects. It will forestall encroachment of the lesion on vital structures in the neck, especially the trachea, it will facilitate Roentgen treatment of the remaining tumor; and it may, when coupled with removal of the normal gland, make possible the use of radioactive iodine. (Total thyroidectomy designed to potentiate the uptake of radioactive iodine in distant metastases will be discussed subsequently.) Wide operative intervention in the neck has been greatly extended by the liberal or routine use of tracheotomy and the control of cerebrospinal fluid pressure; it may be even more so with the employment of freeze-dried arterial grafts to bridge defects in the carotid artery.

Roentgen irradiation is of definite value in the therapy of inoperable tumors, in particular the small cell variety of the highly malignant cancers, and papillary carcinomas. The sensitivity of thyroid carcinomas can be expected to diminish with increasing differentiation. The treatment of bony or pulmonary metastases of follicular tumors is as a rule of little success. This would tend to cast some doubt on the efficacy of prophylactive postoperative irradiation[48]. Comparable data are difficult to obtain. At the Hospital of the University of Pennsylvania our data imply no distinct benefit from the use of prophylactic irradiation in the treatment of encapsulated cancer of low degree of malignancy but clinical observation supports its use for the more malignant lesions. This is substantially the opinion of Hare[47] and others[9,94,101]. Certainly, when used, cancericidal doses should be delivered, in the range of 6000 r. in air. If subsequent data bear out the contention that postoperative irradiation offers a real improvement in survival rate, it will raise the question whether more extensive operative procedures should not also be regularly employed.

Radioactive iodine has introduced one of the most fascinating therapeutic agents on the cancer scene. It is pos-

sible only to survey the vast literature which this isotope has stimulated. In principle, radioactive iodine acts by virtue of the physiologic activity of the thyroid cell in absorbing iodides from the blood stream, concentrating, oxidizing, and fixing them, and retaining the thus formed thyroid hormone in the follicular colloid[49]. To the extent to which the malignant cell has retained these properties, isotopic iodine can be introduced specifically into this cell, where it will during its decay deliver gamma radiation. In 1944, Frantz and associates reported a case of metastatic thyroid cancer which had demonstrated these properties, absorbed radio-iodine, been subjected to internal irradiation, and undergone a dramatic resolution[34,54]. Since this a number of similar reports have appeared[18,38,83,84,86].

Radio-iodine is not proposed as a substitute for the surgical therapy of cancer. Tissue diagnosis must be obtained; primary lesions are infinitely better treated operatively; and the material is not without hazard. It is applicable to those cases with distant, or inoperable local, spread (and possibly, as has been recently advanced, as a postoperative measure comparable to prophylactic external irradiation). Its use is limited to those tumors which have maintained the properties of the normal gland of avidity for, and retention of, iodine, which correlate fairly well with follicular structure and colloid formation[4,35,66]. It is evident, therefore, that only a selected group of well differentiated tumors, which have spread beyond the gland, will prove suitable for therapy. Unfortunately this group has been relatively small.

The iodine avidity of carcinoma cells can best be ascertained by radioautography: radiation within the cells in a tissue section causes darkening of a photographic film[45]. The presence of radio-iodine is not enough, however; the concentration must be adequate to lead to cytotoxic radiation, and it must be uniformly distributed, since gamma radiation has low penetration, of the order of 2 mm[84]. Some tumors may take up iodine but turn it over so rapidly that it is not present sufficiently long to emanate sufficient irradiation[11,28,74]. In a group reported by Fitzgerald and Foote some uptake could be shown in 46 of 100, but very few had sufficient uptakes to justify administration of a therapeutic dose[33].

Fortunately, this situation can be improved by stimulating the metastases to exert themselves more vigorously in the manufacture of thyroid hormone. Rawson showed that this could be done in certain patients by rendering them hypothyroid by thyroidectomy and following this with a course of thiouracil[76,77]. This method depends on an increase of pituitary thyroid-stimulating hormone in the induced hypothyroid state, and may be augmented by giving exogenous T.S.H. In many cases in which the initial uptake of the tumor was poor, it has been increased to a satisfactory level, and in a few cases this has been possible even when there has been no pre-thyroidectomy uptake at all[16,27,89].

Again, however, the cases have been largely confined to the adenocarcinomas showing a follicular pattern, and malignant adenomas[74,81]. There is also some evidence that continuous thyrotropic hormone stimulation may increase the rate of tumor growth, so that thyroidectomy on a patient whose tumor failed to take up radio-iodine might act to his detriment[91].

The picture emerging from the studies on radio-iodine has become a good deal clearer. Given metastasizing thyroid cancer, patients with suitable tumor types should be thyroidecto-

mized and maintained on thiouracil for about 6 to 8 weeks, when a tracer dose of radio-iodine is administered and the avidity of the tumor estimated by following the blood level or urinary excretion of radioactivity, or actually measuring the fraction of the dose incorporated per gram of tissue by biopsy.

If this is not adequate (more than 70 to 80% excreted per 48 hours; less than 1/30 of the tracer dose per gram) further thiouracil may be given, or exogenous thyrotropic hormone may be tried. When sufficient function is obtained, a therapeutic dose is given based on the size of the tumor, its avidity, and the limit of safety of total body radiation[65,74]. Since the blood concentration of the dose, at least initially, will be inversely proportional to the uptake of the tumor, the total body tolerance is more likely to be exceeded if large doses are given to patients with poorly functioning tumors[104]. For the same reason, surgical thyroidectomy is preferable to I_{131} ablation, to prevent excessive irradiation[27], and also because sublethal irradiation may impair the iodine-retaining mechanism of the tumor[78].

The effects of radioactive iodine on the human thyroid have been described. They are comparable to irradiation: fibrosis, vacuolization, distortion of nuclei with abnormal chromatin patterns and bizarre forms[28,37,39]. In the rat, large single doses of I_{131} have produced malignant change in a high proportion of instances[41]. The total body effects of I_{131} are usually not significant in the therapeutic dosage range. Transient lymphopenia occurs commonly[88]. There has been one case of a fatal aplastic anemia[52]. Werner cautions against the use of the material in pregnancy, where (again in the rat) cretinism and neoplastic change has occurred in the fetus[90]. Temporary amenorrhea in the human has also occurred, but the effect on ovarian function has not yet been elucidated.

An estimate of the proportion of thyroid cancers which can be treated by radio-iodine depends of course on the distribution of the case material. Fifteen per cent is the figure usually given in the literature, but this means little without an indication of how many patients did not have metastases, and how many who did were best treated surgically. Rawson, Rall and Peacock report 30 cases with distant metastases, 21 of which had significant iodine concentration after thyroidectomy and thiouracil, and were treated with radio-iodine. Ten had a clinical response[78]. There is no published body of data on the follow-up of successfully treated patients as yet.

ETIOLOGY; RELATIONSHIP TO NODULAR GOITER. The problem of the etiology of thyroid cancer revolves at present around the following questions: 1) Do goiters give rise to benign neoplasms? 2) Do benign neoplasms give rise to cancer? 3) Do involutional nodules give rise directly to malignant change? 4) If a significant number of thyroid cancers have actually evolved from non-neoplastic goiters, what factors lead to goiter formation? and 5) What other factors may give rise to cancer?

A relationship of some sort between cancer and nodular goiter rests firmly on clinical grounds. It has long been known that endemic goiter areas have a higher absolute cancer incidence[98]. Moreover, with few discrepancies, the relative incidence of malignancy in groups of nodular goiter from various parts of the country is remarkably uniform. If this incidence were artificially elevated by selection of cases, one would anticipate that as clinicians become more cognizant of the possibility of cancer in malignant nodules, an influx of less selected cases would lower

the percentage of cancer, but far from this being the case, it has, if anything, increased. Thus, though there may well be differences in etiology between endemic and sporadic goiter, both forms are significantly correlated with the presence of cancer.

The clinical observation that sudden change in a goiter of long standing will often represent malignancy is certainly a valid one. It does not so readily follow that the existence of a goiter for a period of years before its excision and diagnosis as cancer, implies malignant change in a benign neoplasm or an involutional nodule. The elapse of time between observation of a mass and excision of a cancer averages about 4 years in a number of reports[9,94]. The slow-growing nature of these lesions makes it difficult to exclude the presence of cancer from the onset, and it may be exceedingly difficult histologically to be certain whether the whole of a given nodule is malignant, or a portion of it benign, especially in view of the close resemblance to normal thyroid many of these lesions show. The pathologic study of thyroid cancers will turn up a few cases where an apparently benign lesion has undergone malignant change[5,22], but more often this is not demonstrable, and frequently the tumor seems to have been malignant from its onset. From the clinical point of view, therefore, the relationship of nodular goiter to malignancy is clear, but the sequence through adenoma is not so obvious[25,101]. Meissner and McManus comment that the average age at diagnosis of adenomas and carcinomas (except for the anaplastic lesions) is identical, and that whereas papillary lesions predominate among the malignant tumors, they make up only a minority of the benign ones[67]. It should also be pointed out that even the "solitary" nodules, in which the incidence of malignancy is unquestionably high, are often not true adenomas; multiple nodules not detectable clinically may prove to be present, or the lesion may simply be involutional[32]. In the series from the Hospital of the University of Pennsylvania adenomas outnumbered carcinomas by less than two to one[51]. It is safe to assume then, that nodular goiters provide a soil for neoplastic change, benign or malignant, but it is certainly not demonstrated, as commonly stated, that 80 to 90% of cancers arise from true adenomas[58].

The formation of nodular goiters implies that areas within the thyroid respond to certain stimuli in different fashion than the remainder of the gland substance. In this connection the study of the evolution of nodular goiter by Taylor is of interest[92]. The progression is traced through simple diffuse goiter, showing excess iodine uptake, to a stage where the gland shows areas of local hyperfunction, or, more rarely, a solitary hyperactive nodule. Following this the hyperactive nodules undergo hemorrhage and central necrosis, and subsequently become inactive, their function being replaced by other hyperactive areas. Nodularity commences at about age 25, and multiple nodules are present by 40, the proportion of inactive to active nodules increasing with age. Such changes must be initiated and to some extent sustained by a goitrogenic agency; since the work of Marine and Lenhart[64] iodine deficiency has been prominently implicated. Endemic goiter appeared to be satisfactorily explained on this basis, though sporadic goiter is less so. Actively goitrogenic principles have been suggested for many years to reconcile this and other discrepancies[61,64]. It is now generally accepted that many dietary substances have goitrogenic properties[60,99], and that most of these act by reducing the level of iodine in the thyroid gland and reducing circu-

lating thyroid hormone, thereby inducing the pituitary to secrete thyrotropic hormone and resulting in thyroid hypertrophy. Such substances probably must augment the iodine deficiency in goiter areas.

On an experimental basis, using the rat, the action of goitrogens has been shown conclusively to induce malignant change[68], proceeding through a phase analogous to goiter formation in man[44,56,61,75]. Two findings are of especial interest, first that the addition of a carcinogen greatly accelerates the process[2,29] and second that continuous pituitary stimulation is necessary in order to transplant these tumors, which were otherwise morphologically malignant[69].

Summary. From the general picture we may conclude:

1) Thyroid cancer has a definite relationship to involutional change in the gland, and must be ruled out in any adult with a nodular thyroid, and anticipated in any youth with palpable abnormality.

2) Although many, if not most, thyroid cancers are of lower malignancy than cancers at other common sites, they nevertheless have lethal potentialities which should not be ignored.

3) The pathologic classification of thyroid cancer is tending to simplify in the light of more information on clinical behavior and on the degree of physiologic differentiation as determined by radio-iodine.

4) The surgery of thyroid cancer is inclining toward a more radical approach, with neck dissection usually employed in the presence of cervical node metastases, and more commonly as a prophylactic measure.

5) External irradiation is of value in the treatment of some inoperable tumors, and probably as a prophylactic postoperative measure. Internal irradiation with isotopic iodine, emerging from the experimental stage, has a restricted but unquestionable field of usefulness the confines of which are becoming increasingly distinct.

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OPHTHALMOLOGY

UNDER THE CHARGE OF

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PSEUDOTUMOR CEREBRI

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IN a certain number of patients who come to the ophthalmologist with the complaints of headaches and disturbances of vision, edema of the optic disks will be found. In some of this group, consideration of the history and of the demonstrable changes in the vision and visual fields will eliminate the possibility of optic neuritis and establish the diagnosis of papilledema or choked disk. As is well stated by Yaskin, Groff and Shenkin[42], "Every case of papilledema with or without other evidence of increased intracranial pressure should be suspected from the start as harboring an intracranial space-taking lesion until proven otherwise." However, it is known that in some cases of bilateral papilledema exhaustive and repeated neurologic and neurosurgical examinations fail to demonstrate the presence of such a lesion. The favorable outcome of most of these cases is further evidence of the absence of an intracranial neoplasm. Patients who present this syndrome are of particular interest and concern to the ophthalmologist from the standpoints of determining the probable mechanism of production of the papilledema and of the methods of treatment to be employed to forestall, if possible, the development of secondary optic atrophy and consequent permanent loss of vision.

Some authors tend to include in the cerebral pseudotumor group cases which present evidences of inflammatory disease of the central nervous system. It may be more logical, however, to make the diagnosis of pseudotumor only in cases in which, in the words of Walsh[40], "No explanation can be given for the symptoms and signs which suggest the presence of cerebral tumor." Only in this way will it be possible to collect data which may ultimately lead to the determination of the mechanism concerned in the production of the typical syndrome of bilateral papilledema, a normal or smaller than normal ventricular system and a cerebrospinal fluid normal except for increase in pressure.

The confusion which may arise in attempts to interpret the pseudotumor syndrome, if cases with cytologically or chemically abnormal cerebrospinal fluids are included, is illustrated by two articles appearing in recent oph-

*The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

thalmologic publications. Giller and Cogan[16] reported 7 cases under the diagnosis of meningeal hydrops, which they consider to be synonymous with pseudotumor cerebri. This term (meningeal hydrops) was introduced originally by Passot[29] to designate cases, occurring as complications of otitis media, in which the symptoms resembled cerebral tumor more than meningitis and in which the cerebrospinal fluid was normal except for the increased pressure. Passot thought that there was an excess of fluid in the subarachnoid space in these cases. Giller and Cogan[16] stated that the cerebrospinal fluid is clear, the pressure elevated, with *usually* no abnormality in cells or protein. Some degree of pleocytosis or increase in protein content was observed in 4 of their cases, though they noted in their résumé that no significant increase of cells or protein was present except temporarily after ventriculography or repeated spinal punctures. Posner[30] reported an interesting case of "transient glaucoma associated with meningeal hydrops" in which the papilledema receded and the symptoms cleared after repeated spinal punctures. Ventriculograms were normal, but the cerebrospinal fluid contained 31 lymphocytes per cubic millimeter and 70 mg. protein per 100 cc., and a smear of the ventricular fluid revealed Gram-positive bacilli, and a culture, *Bacillus subtilis*. If any significance is ascribed to this last finding, the case can hardly be considered one of pseudotumor in the narrower sense.

According to Ray and Dunbar[32], the term "pseudotumor cerebri" was introduced by Nonne[28] in 1914 to designate a syndrome which he[27] had described in 1904 as a more or less chronic development of the picture of brain tumor with or without localizing signs and without demonstrable pathologic changes. The group of 22 cases reported by Frazier[13] under the title of cerebral pseudotumor in 1930 was a rather heterogeneous one and included cases which today would probably not be so classified. In some instances roentgenograms of the head were abnormal and localized encysted collections of fluid were present. In at least one of the cases papilledema was not present. Pleocytosis in the cerebrospinal fluid was said to be not uncommon in the group. The presence of dilatation of the ventricles was not thought to militate against the diagnosis of pseudotumor. The long duration of the symptoms and the benign course of the disease were the chief features by which the diagnosis of pseudotumor was established. Nineteen of Frazier's[13] 22 patients were alive 1 to 25 years after they were first studied and all but 4 had been observed for more than 2 years, "a period which has been proposed as a criterion by which to exclude tumor proper."

Among the terms considered by Giller and Cogan[16] to be synonymous with meningeal hydrops and pseudotumor cerebri is "otitic hydrocephalus." Though Walsh[40] in his text devoted separate sections to otitic hydrocephalus and to pseudotumor cerebri and stated that dural sinus thrombosis should be differentiated from pseudotumor, and though I am inclined to agree that the two are different entities, it is interesting to try to trace the steps leading up to the concept that thrombosis of the superior sagittal sinus is responsible for the development of the pseudotumor syndrome.

Otitic Hydrocephalus. In 1925, Lillie and Lillie[20] reported 4 cases in which bilateral choked disks were present in association with surgical mastoid disease without apparent intradural involvement and in the absence of lateral sinus thrombosis. The choked disks subsided slowly following

mastoidectomy without further treatment. In 1931, Symonds[37] stated that "As a not very uncommon complication of otitis media there may occur a state of increased intracranial pressure due to the presence of an excess of normal cerebrospinal fluid." He thought that the cause of this increase of cerebrospinal fluid was obscure and he suggested the name "otitic hydrocephalus" because this term would not imply an inflammatory process and also would not specify whether the excess fluid was present in the ventricles or in the subarachnoid space. One of Symonds'[37] patients had an infected lateral sinus thrombosis, another an extradural abscess following a mastoidectomy for recurrent chronic mastoiditis and the third had had acute otitis media 6 weeks previously. The symptoms and signs of otitic hydrocephalus as described by Symonds[37] are practically identical with those of pseudotumor cerebri: intermittent headache, papilledema, occasionally lateral rectus paralysis and increased cerebrospinal-fluid pressure in a patient who looks well.

In 1937, Williams[41] stated his opinion that otitic hydrocephalus was not a distinct entity but was only one form of the acute or subacute hydrocephalus which might be produced by involvement of the arachnoid by bacteria or toxins from any source. This concept was very similar to that of McAlpine[24] who introduced the term "toxic hydrocephalus" because he thought that the designation "otitic" was too limited, since the same syndrome might follow infections other than otitis media and mastoiditis. He reported 5 cases following nasopharyngeal infection in which the main clinical features were "advanced papilledema in association with a general state of physical fitness, an alert mind, the absence of any localized signs, and a normal spinal fluid apart from a greatly increased pressure."

Williams[41] thought that the hypothesis that the hydrocephalus was produced by interference with the mechanism of absorption of the cerebrospinal fluid was the best documented and he suggested that the pressure of the hydrocephalus on the cranial sinuses, especially at their exits through the cranium, might cause a continuation of the hydrocephalus by mechanical means. On the other hand, McAlpine[24] thought that the basis of the hydrocephalus was the overproduction of cerebrospinal fluid as a result of a functional disturbance of the choroid plexus. In his opinion, the negative Queckenstedt, the free flow of fluid and the normal ventricles in these cases indicate that the fluid is accumulated outside of the ventricular system. It is of interest to note that in both of the cases reported by Williams the lateral sinus was not thrombosed, unless thrombosis developed after surgical treatment in the second case.

Papilledema in Association With Lateral Sinus Thrombosis. It is a recognized fact that papilledema can develop as a result of thrombosis of the sigmoid or lateral sinus. Dill and Crowe[10] stated that among 26 patients with thrombosis of the sigmoid or lateral sinus, choked disks were found in 12, unilateral in 2 and bilateral in 10. They thought that the unilateral choked disks were due to involvement of the cavernous sinus and the bilateral to increased intracranial pressure. However, the cerebrospinal-fluid pressure was determined in 6 of the cases with bilateral choked disks and was found to be elevated in 3 and normal in 3. According to Williams[41], Cairns[4] reported in 1930, under the name of "serous meningitis or arachnoiditis" a group of cases similar to those later called "otitic hydrocephalus" by Sym-

onds[37], but not necessarily secondary to middle ear or mastoid infection. In one of his cases, the left lateral sinus may have been thrombosed, since there was no rise in the pressure of the cerebrospinal fluid when the left jugular vein was compressed (the Tobey-Ayer test).

In 1936, Ersner and Myers[11] stated: "In a previous publication we suggested that venous stasis of the intracranial circulation may prevent absorption of the cerebrospinal fluid. This stasis may be produced by disease either in the mastoid process or other parts of the temporal bone or by anomalies of the cranial veins. Roentgenologically, some of these cases presented variations in the size of the lateral sinuses and jugular foramina." These authors reported a case in which the right lateral sinus was obliterated following thrombosis complicating acute mastoiditis. The left lateral sinus was found to be smaller than the right. In subsequent episodes of acute otitis media on the right, the patient would have headache, drowsiness, nuchal rigidity and choking of the right optic disk. In another case, choking of the right disk and lateral rectus paralysis developed after obliteration of the right lateral sinus for phlebitis. In both cases, the symptoms were relieved by dehydration and lumbar puncture. Ersner and Myers[11] thought that these observations corroborated the hypothesis that intracranial circulatory disturbances were important factors in the production of otitic hydrocephalus.

Shapiro[36] reported a case in which, after radical mastoidectomy and labyrinthectomy, removal of a clot from the right lateral sinus and ligation of the right jugular vein, headaches and choked disks developed which receded without specific treatment. As there was no inequality in the jugular foramina, Shapiro[36] postulated an arachnoiditis in the posterior fossa. However, Greenfield[17] pointed out that changes in the ocular fundi occurred in 8 of his 22 cases of thrombophlebitis of the lateral sinus and might precede more pathognomonic signs. Full veins on the affected side were present in 2 cases, blurring of the margins of both disks in 3 and elevation of the nerve heads in 3.

Ford and Murphy[12] reported the case of a girl, aged 7 years, in whom headache, vomiting, papilledema and left lateral rectus paralysis developed one week after an attack of acute otitis media in the left ear. A ventriculogram revealed small, symmetrically placed ventricles. A right subtemporal decompression was made. The papilledema receded and the girl remained well for 2 years. Then acute left mastoiditis was followed by fatal meningitis. Necropsy revealed, in addition to the recent meningitis, that the left lateral sinus was replaced by a fibrous cord with a few small vascular channels running through it. This was interpreted as organization and partial recanalization of a thrombus which had occurred 2 years before and which was responsible for the development of increased intracranial pressure at that time.

Thrombosis of the Superior Longitudinal or Sagittal Sinus in Otitic Hydrocephalus. In 1937, Frenckner[14] described a case in which headache, diplopia and bilateral papilledema developed following radical mastoidectomy for chronic otitis media. The cerebrospinal fluid was found to be under a pressure of 350 mm. of water. A sinogram was attempted by injection into the posterior part of the superior longitudinal sinus, but no blood could be withdrawn from the sinus. Later, by carotid angiography, a phlebogram was obtained which revealed the presence

of obstruction of the posterior part of the superior longitudinal sinus.

In 1937, Bailey and Hass[1] reported a case studied at necropsy which showed the sequence of otitis media, lateral sinus thrombosis, retrograde propagation of the thrombus into the superior longitudinal sinus and obstruction of tributary cerebral veins with resultant hemorrhages and necrosis of the brain. They thought that their cases demonstrated that thrombosis of the superior longitudinal sinus was not invariably a fatal lesion and that thrombi in this sinus could become organized and canalized.

Also in 1937, in a further discussion of otitic hydrocephalus, Symonds[38] stated: "It is suggested that mural thrombophlebitis of the superior longitudinal sinus, by retrograde extension from the lateral sinus, may, by putting out of action a sufficiently large proportion of the arachnoid villi, be the cause of otitic hydrocephalus." Symonds[38] took note of the fact that the suggestion had been made that obstruction of the lateral sinus might in itself be responsible for an increase in intracranial pressure. He thought this unlikely, because lateral sinus thrombosis is a rather common complication of otitis media and hydrocephalus is rare, and also because hydrocephalus may occur when, as judged by the Queckenstedt test, both lateral sinuses are patent. However, he agreed that the incidence of lateral sinus thrombosis in cases of otitic hydrocephalus was rather high. In his 12 cases of otitic hydrocephalus, lateral sinus thrombosis was proved in 5 and probable in 3 others. He thought that, anatomically, superior longitudinal sinus thrombosis should be more likely to occur in cases of involvement of the right lateral sinus. He found that among 26 collected cases of otitic hydrocephalus following unilateral otitis media, the right ear was involved in 17 and the left ear in 9.

Symonds[38] stated that, in cases of fatal occlusion of the superior longitudinal sinus, erythrocytes are found in the cerebrospinal fluid and, in some instances, there is gross subarachnoid bleeding. In his words,

> "There is a discrepancy here between the frequent presence of blood in the cerebrospinal fluid in cases of proved thrombosis of the superior longitudinal sinus, and its absence in the cases of otitic or infective hydrocephalus in which the writer has suggested thrombosis of that sinus as the cause. It is possible, however, that this discrepancy may depend upon the fact that in the former group, with the exception of two cases, the proof of longitudinal sinus thrombosis was obtained only at postmortem. In the fatal cases with extensive occlusion of the sinus there is nearly always occlusion, if not thrombosis, of the large, middle group of superior cerebral veins, and with this often subarachnoid hemorrhage, and areas of red softening in the brain. The degree, extent and localization of thrombosis in the superior longitudinal sinus resulting in a bloodstained cerebrospinal fluid may be those which usually result in death before hydrocephalic symptoms have had time to appear."

Gardner[15] objected to the term "otitic hydrocephalus" because, he pointed out, encephalographic studies will not permit a diagnosis of hydrocephalus. Although there may seem to be an increased amount of fluid in the ventricles by ventricular estimation, the ventricles are actually normal or smaller than normal in size. He did not think that there was a true increase in the amount of cerebrospinal fluid in these cases. He thought that the increase in intracranial pressure was caused by interference with the outflow of venous blood from the cranial cavity, and that recovery from the state of increased intracranial pressure occurred "when, by means of recanalization or the development of collateral supply, the return of venous blood from the cranial cavity is once more adequate." He

reported 10 cases in which increased intracranial pressure persisted from 1 to 11 months after acute otitis media. The presence of lateral sinus thrombosis was proved at mastoidectomy or at necropsy in 5 cases and was suggested by the Tobey-Ayer test in 3 others. Necropsy in 2 cases showed extensive thrombosis of the dural sinuses including the longitudinal sinus. However, Gardner[15] did not think that it was necessary for the development of the syndrome that the superior longitudinal sinus be thrombosed.

Thrombosis of the Superior Longitudinal or Sagittal Sinus in Pseudotumor Cerebri. In his 1937 paper in which he stated his belief that otitic hydrocephalus was really a symptom of superior longitudinal sinus thrombosis, Symonds[38] reported 3 cases which presented the syndrome of otitic hydrocephalus but in which the primary source of infection was not in the middle ear. In 1941, Martin and Sheehan[23] reported an interesting case which, though not classified as pseudotumor cerebri, gave support to the concept that obstruction of the superior longitudinal sinus could lead to an increase in intracranial pressure. A woman, aged 32 years, 14 days after delivery developed weakness of the left arm, paralysis of the left side of the face and slight weakness of the left leg and had repeated convulsions during a 24-hour period. The cerebrospinal fluid was under normal pressure but was slightly bloody. No further symptoms developed for 2 weeks but then convulsions occurred daily for 3 days. The cerebrospinal-fluid pressure rose to 240 mm. of water, and headaches and papilledema developed. On the 69th day of the illness, exploratory craniotomy revealed an organized occluded vein in the fissure of Rolando and some softening of the cerebral cortex. The patient left the hospital 1 month later without disability. The authors explained the rise of intracranial pressure on the basis of occlusion of the superior longitudinal sinus secondary to thrombosis of the right rolandic vein with resultant obstruction to absorption of the cerebrospinal fluid by the pacchionian bodies and the superior longitudinal sinus.

In 1948, Lima[21] stated that occlusion of large intracranial arteries, especially the sylvian arteries, may be demonstrated by arteriography in patients whose clinical histories suggest cerebral tumor and some of whom have papilledema. In one of his patients who was suspected of having a brain abscess, angiography revealed occlusion of the superior longitudinal sinus. Lima asserted that, if cerebral pseudotumor is due to cerebral thrombosis, angiography can enable one to make the diagnosis.

In their first paper, published in 1950, Ray and Dunbar[31] deviated somewhat from the usually accepted concept of "pseudotumor cerebri," which is generally regarded as a benign process, by saying that a few patients may die in the acute phase of the disease. They reported the case of a woman, aged 48 years, who had a sudden onset of weakness, vomiting, blurred vision, headache and diplopia. These symptoms persisted for 2 weeks, then regressed, but recurred 6 months later. At this time, the patient presented bilateral papilledema, right lateral rectus paralysis, normal vision and visual fields, normal head rays and electroencephalogram. The cerebrospinal fluid was normal except that it was under increased pressure (480 mm. of water). Three ventriculograms showed small ventricles without distortion or displacement. Carotid arteriograms revealed complete block of the right common carotid artery 2 cm. proximal to its bifurcation. Eight months later

a venogram of the superior sagittal sinus revealed a block at the junction of the middle and posterior thirds of the sinus. The venous pressure in the sinus equaled 480 mm. of saline solution (normal 100 to 150 mm.). Five months after removal of an organized thrombus from the sinus and a short course of anticoagulants, the papilledema had receded and the patient was in good health.

Ray and Dunbar[31] gave three reasons for thinking that obstruction to venous drainage of the brain might be responsible for the syndrome of pseudotumor cerebri: (1) bilateral neck dissections and bilateral ligation of the jugular veins frequently result in papilledema, headache, diplopia and increased cerebrospinal-fluid pressure which may persist for some time; (2) ligation or resection of the posterior two thirds of the superior sagittal sinus during the removal of parasagittal meningiomas may result in coma and death due to massive congestion and hemorrhagic edema of both hemispheres; and (3) thrombosis of the superior sagittal sinus has been demonstrated at necropsy in cases of pseudotumor cerebri.

In a later paper, Ray and Dunbar[32] reported, under the classification of pseudotumor cerebri, 4 cases in which they had carried out sinus venography. Occlusion of the superior sagittal sinus was demonstrated in 3 and occlusion of the dominant transverse sinus in the fourth. They expressed the opinion that most cases hitherto classified as increased intracranial pressure of unknown origin will prove to be instances of thrombosis of the superior sagittal or transverse venous sinuses. They did not agree with Symonds as to the necessity of involvement of the superior sagittal sinus. They thought that the increased intracranial pressure was the purely mechanical result of obstruction of the intracranial venous system and that, therefore, thrombosis of one transverse sinus could lead to increased intracranial pressure if the other transverse sinus was absent or inadequate to serve as a channel for drainage of the superior sagittal sinus. They did not think that it was possible to rule out the presence of thrombosis of the superior sagittal sinus by the Tobey-Ayer test. They advised that, in suspected cases of pseudotumor cerebri, the presence of normal ventricles be established by ventriculography before proceeding with a venogram. The techniques of dural sinus venography were described by Ray, Dunbar and Dotter[33] in another paper.

Hemorrhage in Association With Thrombosis of the Superior Sagittal Sinus. Ray and Dunbar[31,32] suggested the use of anticoagulants in the treatment of patients presenting the pseudotumor syndrome with proved or suspected venous sinus thrombosis. Barnett and Hyland[2] warned of the potential dangers in this type of therapy in view of the known hemorrhagic complications of such thromboses. The characteristic presence of intracranial or subarachnoid bleeding in association with thrombosis of the superior sagittal sinus, particularly in its acute phase, is a rather strong argument against accepting thrombosis of this sinus as the cause of many cases of pseudotumor cerebri, particularly of those in which papilledema is discovered accidentally and is not accompanied by, or historically preceded by, any symptoms of intracranial disease. In Giller and Cogan's[16] seventh case of "meningeal hydrops," repeated spinal punctures yielded a bloody fluid under increased pressure. Necropsy revealed thrombosis of the posterior half of the superior longitudinal sinus and incomplete thrombosis of both lateral sinuses with partial recanalization. These thromboses were estimated as being about

4 months old, corresponding to the onset of symptoms. This case was classified by the neuropathologist as one of cerebral pseudotumor in spite of the presence of a small hemorrhage in the left temporal lobe and a recent cerebellar infarction. It is true that this case was complicated by hypertensive disease which may have been responsible for the more recent cerebral lesions.

On the other hand, Ford and Murphy[12] reported the case of a woman, aged 26 years, who had headache and vomiting for 10 days. She was semistuporous and had bilateral papilledema and lateral rectus paralysis. The cerebrospinal fluid was under great pressure and was blood-tinged. A ventriculogram revealed small and symmetrical ventricles. The patient died following subtemporal decompression. Necropsy revealed extreme congestion and edema of the brain and a partially organized thrombus occupying the entire length of the superior longitudinal sinus with its collaterals, the torcular Herophili and the left lateral sinus. The authors did not classify this case as one of cerebral pseudotumor.

Nevertheless, it seems to have been fairly definitely established that thrombosis of the superior longitudinal sinus can cause edema of the brain and that hemorrhage may not be an outstanding feature of the thrombosis. Thus Holmes and Sargent[18], in commenting on 76 cases of gunshot injury involving the superior longitudinal sinus, said:

"The general symptoms of intracranial pressure have been as a rule pronounced. Most of the patients have suffered considerably from headache, and in some it has been particularly severe. In five cases there was also definite optic neuritis with considerable swelling of the discs, and not merely such congestion and blurring of their edges as is seen in a large proportion of all gunshot wounds of the head. In four of these cases at least we could exclude meningitis and secondary cerebral abscess, and must consequently attribute the ophthalmoscopic changes to the oedema and swelling of the brain."

These authors stated also that the injury usually caused a thrombus in the superior longitudinal sinus with congestion or thrombosis of neighboring cortical veins. The cortex and subcortical white matter were edematous with minute hemorrhages and, in a few instances, softening of the brain tissue near the mesial fissure. Uncomplicated cases, they said, showed a remarkable tendency to improve, probably because free venous anastomosis permitted reestablishment of the circulation. Subdural hemorrhage was rare and, if present, was only a thin film not requiring operative intervention.

Barnett and Hyland[2] stated that many patients with intracranial venous thrombosis are capable of recovery and they added, "The condition may occur in otherwise healthy individuals and we have a growing group of postpartum and 'pseudotumor' cases under observation who have recovered from the effects of the intracranial lesion." They reported a case, arteriographically proved to have a thrombosis of the internal carotid artery, in which the prolonged presence of papilledema in association with normal ventricles led to the assumption of a concomitant thrombosis of the superior longitudinal sinus. They suggested also that the papilledema observed in some cases of leukemia might be caused by thrombosis of the superior longitudinal sinus.

Nielsen and Courville[26] reported their necropsy findings in 43 cases of lateral sinus thrombosis associated with otitis media. In 4, the thrombosis had extended into the superior longitudinal sinus, and in 1, the superior longitudinal sinus was involved along with a number of other sinuses. They studied

also 2 cases with isolated thrombosis of the superior sagittal sinus. They noted the variability and at times absence of symptoms in cases of otitic superior longitudinal sinus thrombosis and concluded that the sinus, if not infected, might be thrombosed without causing any serious cerebral damage. Possibly, if the thrombosis develops gradually, adequate collateral circulation may be established for venous drainage of the cerebral cortex, especially if the anterior portion of the sinus remains patent. Under such circumstances, the only clinical symptoms might be those due to failure of absorption of the cerebrospinal fluid and the resultant increase in intracranial pressure.

In discussing venous thrombosis in the central nervous system, Martin[22] stated that the effects of thrombosis of the sinuses and veins could be determined more readily in aseptic than in septic cases. In general, thrombosis of a sinus without thrombosis of associated veins produced widespread or general obstructive effects such as edema with increase of intracranial pressure. Thrombosis of cerebral veins caused bleeding into the neighboring brain tissue and focal symptoms corresponding to the area of the brain involved. In any particular case, the symptoms and signs might be those arising from either lesion or might be a mixture of the two. An example of such a mixed picture was reported by Russell[34]. Papilledema and increased cerebrospinal-fluid pressure developed on the basis of aseptic, marantic type, sinus thrombosis which began in the right lateral sinus and spread backward into the superior longitudinal sinus as shown at necropsy. Death resulted from perforation of a tuberculous ulcer of the ileum. There was no evidence of intracranial tuberculosis. This was not a typical cerebral pseudotumor, since there was left hemiparesis due to a parasagittal hemorrhagic infarct in the posterior part of the right frontal lobe and there was also mild symmetrical dilatation of the ventricular system.

It is of interest to note that Beck[3] was unsuccessful in his experimental efforts to reproduce the pseudotumor syndrome in animals. He said: "We are forced to conclude that, at any rate in the dog and cat, the greater part of the superior longitudinal sinus can be suddenly obliterated without any gross inconvenience to the animal," and "It is possible that a condition analogous to that of 'otitic hydrocephalus' in man can only be produced experimentally by inducing a thrombosis that will spread from the main sinus into the adjacent lacunae and the mouths of the venous tributaries."

Intracranial Hypertension of Unknown Cause. It is possible that this is the most satisfactory term at present available for the designation of the group of "pseudotumor cerebri" cases with which the ophthalmologist is most concerned. Ford and Murphy[12] thought that cases of dural sinus thrombosis should be differentiated from the cases described by Dandy[5] as brain swelling of unknown origin. As previously mentioned, Walsh[40] agrees with this point of view. As summarized by Ford and Murphy[12], the salient features of this syndrome are: papilledema and other signs of increased intracranial pressure in previously healthy persons with the cause completely obscure; no signs of focal damage to the brain and the mental state clear except when the intracranial pressure is very high; cerebrospinal fluid under increased pressure but otherwise normal; ventricles small and symmetrically placed as if they were compressed by general swelling of the brain; after subtemporal decompres-

sion, bulging which usually disappears in a few weeks but may recur at intervals for several years; prognosis good except for possibility of optic atrophy; no cause found even at necropsy. Kehrer[19] also stated that the processes which give rise to cerebral pseudotumor are unknown and that even the most precise histologic investigation reveals no pathologic alterations.

In 1937, Dandy[5] reported 22 cases of this type. He thought that the increase in pressure must be dependent on an increase in the intracranial fluid content, and that this fluid must be in the brain and not in the meningeal spaces, since the ventricles are small and the pressure is not relieved by the evacuation of fluid from the subarachnoid spaces. An alternative explanation might be variations in the intracranial vascular bed under vasomotor influences. Dandy[5] thought that the normal response obtained to the Queckenstedt test ruled out the possibility of obstruction in the large venous sinuses. The cerebrospinal fluid was normal except for increased pressure in all but 2 of Dandy's cases. All the patients recovered completely.

Davidoff and Dyke[7,8] reported 15 similar cases, in 1936 under the title of "serous meningitis" and in 1937 under the title of "meningeal hydrops." One of their cases had 66 cells and another 75 mg. total protein per 100 cc. in the cerebrospinal fluid. In the other cases the cerebrospinal fluid was normal except for increase in pressure. All of their patients improved under treatment. One patient died at home from another cause; examination of the brain showed nothing except questionable pericellular and perivascular edema. The authors thought that recovery was dependent on the reestablishment of normal equilibrium between production and absorption of cerebrospinal fluid. However, in 1947, in his discussion of a presentation by Yaskin, Groff and Shenkin[42], Davidoff[6] stated that he was inclined to agree with Symonds[38] that an incomplete thrombosis of the dural sinuses is the factor that prevents proper absorption of the cerebrospinal fluid and creates the imbalance which results in increased intracranial pressure and papilledema.

In 1939, Sahs and Hyndman[35] reported 5 cases under the alternative terms of "intracranial hypertension of unknown cause" and "cerebral edema." They demonstrated the absence of hydrocephalus and of postencephalitic cortical atrophy by air studies. They thought that extracellular and intracellular edema of the brain, questionably of toxic origin, was present rather than excessive production or diminished absorption of cerebrospinal fluid.

In 1947, Yaskin, Groff and Shenkin[42] reported 12 cases of papilledema in which they were not able to demonstrate the presence of tumor, abscess, subdural hematoma, arachnoiditis, otitic hydrocephalus or nonsuppurative encephalitis. Although the cerebrospinal fluids contained no cells, they entitled their paper "Severe Papilledema in Diffuse Infections of the Nervous System," since they thought that the principal mechanism involved was an alteration of fluid exchange, probably on an infectious basis. Because of the mental alertness of the patients, they doubted the presence of severe edema of the brain. They stated, "There are patients who have papilledema and other evidences of intracranial pressure probably due to alterations of cerebrospinal fluid circulation and/or chemical composition of the fluid, the nature of which is unknown."

Cerebral Edema and the Pseudotumor Syndrome. Devanney and Shea[9] reported an interesting case of a boy, aged 9 years, with a history of

many allergies and infections. Three and a half years earlier he had had a short episode of headache, lethargy, blurred vision, diplopia and papilledema which cleared spontaneously. Following an attack of otitis media, headache and papilledema again developed. The vision and fields of vision were normal. The cerebrospinal fluid was under increased pressure but was otherwise normal. A ventriculogram was normal. With Benadryl and measures for the control of his allergies, the papilledema receded and the child has remained well for 3 years. The authors stated: "This observation suggests that allergy must be considered in the differential diagnosis of that vague group of disturbances classified as pseudotumor or encephalopathy of undetermined cause."

It is rather striking that in 30 of the 42 cases (71.4%) reported by Dandy[5], by Davidoff and Dyke[7,8] and by Sahs and Hyndman[35], the patients were women. The exact significance of this observation is not clear. It may or may not imply a relationship with the reported instances of papilledema associated with "menstrual edema." Thomas[39] reported the case of a woman, aged 38 years, who at each menstrual period would develop severe generalized edema with a gain of weight of 11 to 14 pounds, blurred vision, choked disks, headache and an increase in cerebrospinal-fluid pressure with an otherwise normal fluid. All symptoms and signs would recede rapidly after the spontaneous occurrence of diuresis. McCullagh[25] reported the case of a woman, aged 24 years, who had had for 5 years headache, which usually occurred shortly before or shortly after the onset of menstruation, and had diplopia for 3 weeks. She had had otitis media 4 years before, but there had been no evidence of lateral sinus thrombosis. Papilledema of 3 diopters was present. The visual fields were normal except for enlargement of the physiologic blind spots. Examination of the nervous system revealed no abnormalities. A ventriculogram and an encephalogram were normal. The cerebrospinal fluid was under a pressure of 450 mm. of water but was otherwise normal. Administration of a pregnancy urine extract seemed to help both Thomas'[39] and McCullagh's[25] patients. But McCullagh used also repeated spinal punctures and dehydration measures in the treatment of his patient. The fundi of McCullagh's patient were normal at the end of 4 months and were still normal 15 months later. Thomas[39] suggested that the edema and diuresis were probably functions of tissue thirst, depending on hydrophilic tissue states or the reverse. McCullagh[25] surmised that the edema might depend on the influence of the steroid hormones on the retention of sodium, chloride, other electrolytes and water in the body.

The treatment recommended by most authors in these cases of presumed edema of the brain consists of limitation of fluid intake, dehydration, and spinal punctures repeated as seems necessary to control the cerebrospinal-fluid pressure. If these measures fail to produce satisfactory recession of the papilledema, subtemporal decompression is advised, especially if loss of vision from secondary optic atrophy seems to be impending. Dandy[5] did subtemporal decompression in 18 of his 22 cases. Davidoff and Dyke[7,8] did decompressions in 14 of their 15 cases, subtemporal in 13 and suboccipital in 1.

Comment. It seems probable that most cases of the true "pseudotumor cerebri" syndrome with normal ventricular systems and chemically and cytologically normal cerebrospinal fluids are instances of cerebral edema.

It seems to be true that edema of the brain can be caused by thrombosis or thrombophlebitis of the dural sinuses, especially if the superior longitudinal sinus is involved. However, it should be recognized that cerebral edema can be caused also by other factors. Therefore, unless there is a definite preceding or associated process in which sinus thrombosis might be expected to occur, it would seem logical to study the patient carefully for all other possible causes of the edema before making a presumptive diagnosis of superior longitudinal (or sagittal) sinus thrombosis.

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NEUROLOGY AND PSYCHIATRY

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A REVIEW: PSYCHOLOGICAL RESPONSES TO ACTH, CORTISONE AND RELATED STEROID SUBSTANCES

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THE original preliminary report[16] on the effect of "Compound E" and of ACTH on 16 cases of rheumatoid arthritis included the following significant comments: "Several patients stressed the loss of the 'toxicity' of the disease and experienced a marked sense of well-being. This euphoria apparently represented not mere relief of pain but a positive factor accompanied by increased mental capacity and activity, sometimes to the point of mild 'comfortable' insomnia. Having in mind the field of mental illness, we called the attention of our psychiatric colleagues to this euphoria and they are carrying out a series of observations regarding it." Since that time a host of investigators have made further observations and studies of the psychological responses to ACTH, cortisone and related steroid substances.

One early report[35] noted that 66% of a group of 21 patients treated with ACTH experienced "a marked sense of well-being." Other reports[2,3,13,26,40] were rapidly confirmatory of this finding in the ACTH treatment of such diseases as rheumatoid arthritis, gout, lupus erythematosus, asthma, acute serum reactions, and periarteritis nodosa. This bright picture was almost simultaneously darkened somewhat by reports such as that of Soffer and associates[34] which stated that 17% of a group of patients with acute disseminated lupus erythematosus experienced "a more striking alteration in mood characterized by severe depression and apathy." Taylor and Morris[36] found 2 hypomanic reactions, 1 schizoid reaction with catatonic features, and 1 paranoid disorientation in a series of 5 patients with malignant disease treated with ACTH. Another report[7] described "a mild maniacal state," and 2 "near-maniacal states" occurring in patients with chronic ulcerative colitis. Other typical reports warned that some patients become frankly psychotic when treated with cortisone[6,8,11,38]; that one case of "severe mental depression" occurred in a group of 11 patients under treatment for acute rheumatic fever and rheumatic carditis[27]; and that a case of severe agitated depression developed during a course of ACTH therapy and persisted for several weeks until terminated by electroshock treatment[23]. The variety of un-

desirable reactions reported also included the rare precipitation of convulsive seizures[28], at times with a fatal result[12].

Rome and Braceland brought some order into the classification of psychological responses to ACTH and cortisone by dividing the range of responses into 4 descriptive grades[29,30,31]. Grade 1 encompasses those mild reactions described by patients in the following typical statements: "I never felt better in my life!" "I'm on top of the world!" "I feel wonderful!" They feel buoyant. Many patients state that their thinking is accelerated. A Grade-2 response is merely a more marked response than Grade 1. These patients are voluble and often given to hyperbole. Physical as well as mental stimulation is apparent. They are active to the point of restlessness. Insomnia is common and is refractory to the usual nightly sedative. Appetite and muscular strength are vastly improved. The mood elevation approaches the hypomanic level and there may be some flight of ideas. Approximately 60% of their patients who were treated with cortisone and ACTH showed psychological responses in Grades 1 and 2. Grade 3 comprises every other variety of response short of overt psychosis and includes ideational and behavioral changes as well as mood excursions such as depression. These patients are profoundly affected by lethargy, indifference, depression, agitation, excitement, marked anxiety, rumination or obsessional preoccupation. Approximately 25 to 30% of their patients experienced reactions that have been graded as 3. They were impressed by the fact that Grade-3 responses usually existed in either a latent or mildly overt form prior to the administration of ACTH or cortisone. Grade-4 responses meet the diagnostic criteria of psychotic reaction types. The prepsychotic personality seemed to be of paramount importance in determining the form of the psychotic response. In this group are found all the usual psychotic reaction types. Most patients who have a Grade-4 response give a history of previous psychiatric illness of some sort, but not necessarily of a previous psychotic illness. In their series Grade-4 reactions occurred in 10% of their patients.

There is some partial disagreement among various investigators of the psychological responses to ACTH and cortisone. All agree that the euphoria in chronically ill patients is due, at least in part, to the associated dramatic physical improvement. Clark, Bauer, and Cobb[4] could find no characteristics of premorbid personality that might enable one to anticipate the occurrence or predict the severity or duration of psychiatric complications in a given case. In addition they found no correlation between the severity or duration of the psychoses and the total or average daily dose of ACTH. Rome and Braceland[32], on the other hand, state that, "all of the patients in whom psychologic responses graded 3 and 4 have developed, have made more or less marginal psychologic adjustments prior to their treatment with these substances. As such, they are inherently vulnerable to what for them is the constancy of the internal environment." Again, they believe that "the total dose and the total amount of hormone used, as well as the rate at which the daily dose is increased or decreased, bears a direct relation to the psychologic responses observed." Thorn *et al.*[37] report that in their experience psychoses have developed only in the treatment of diseases known to produce organic changes in the central nervous system, thereby making the

role of the drug difficult to assess. Lidz *et al.*[22] found no overt psychoses in over 350 patients with diverse illnesses who had been treated with ACTH or cortisone. The same authors conclude that the emotional response of euphoria is always in keeping with the amelioration or cessation of physical symptoms and that it never occurred during courses of treatment which failed to produce definite physical improvement. Hench *et al.*[17] were impressed by the euphorigenic capacities of cortisone itself.

The discovery that ACTH and cortisone administration is often followed by overt personality disorders resembling schizophrenia as well as mood changes similar to those of the affective psychoses[4,5], has stimulated further research into the pituitary-adrenal system. At the present time there is no complete explanation of the mechanism underlying the secretion of anterior pituitary hormones. Harris[14] and Hume[21] have shown that hypothalamic stimulation may cause a release of ACTH and that this is prevented by complete stalk section. Yet, anterior pituitary tissue transplanted to the anterior chamber of the eye will still release ACTH under appropriate stimulation[10,24], thereby indicating the possible importance of humoral mechanisms. A rapid release of ACTH may occur under certain stress conditions, possibly due to epinephrine[33] acting directly on the adenohypophysis or through the hypothalamus[21].

Recently, there has been a renascence of interest in Cushing's syndrome because of the similarity between it and states of hyperadrenalism induced by ACTH and cortisone. It is noteworthy that mental symptoms (including psychotic reactions[39]) occur at times with both conditions.

Studies of male schizophrenics[9,15,20] following both physiological and psychological stress, demonstrate that they display less adrenal responsivity than a comparable group of normal men of the same age range. Measures of percentage change with stress from resting levels of 17-ketosteroids, sodium, potassium and uric acid reflect this relative unresponsivity. There is a similar type of subnormal responsivity to injected ACTH on the part of male schizophrenic patients[20]. It was found that the more normal the response of the adrenal to test injections of ACTH, the better the prognosis when the patient is subsequently given electroshock therapy[18]. A group of female patients suffering from involutional depression showed improvement in the stress response of the adrenals following successful electroshock treatment[19].

A number of years ago Allen and Broster[1] described relief from schizophrenia in several cases following the removal of one overactive adrenal. In addition, ACTH and cortisone have been found to be ineffective in the treatment of schizophrenia and the affective psychoses[8,25].

In conclusion, it is obvious that the final determination of the true relationship of the pituitary-adrenal system to psychological responses must await the combined efforts of many branches of medicine and surgery as well as the basic medical sciences. This is logical and to be expected, as feelings and emotions represent total-body reactions rather than isolated phenomena such as smiling with the lips (when happy) or clenching the fists (when angry).

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BOOK REVIEWS AND NOTICES

PSYCHONEUROTIC ART: ITS FUNCTION IN PSYCHOTHERAPY. BY MARGARET NAUMBURG, Department of Clinical Psychiatry, New York State Psychiatric Institute. Pp. 148; 46 ills. New York: Grune & Stratton, Inc., 1953. Price, $6.75.

THE author presents the 3-year study of the psychotherapeutic significance of the spontaneous art productions of a psychoneurotic patient. In addition, there are sections on the theory and practice of art therapy, a review of the history and development of art in therapy and a consideration of some of the recent literature on clinical and theoretical aspects of spontaneous art in therapy and diagnosis.

The author suggests that the expression of conflict by means of spontaneous art at the pre-verbal level frequently by-passes the ego censorship in a way that verbal communication cannot. In addition, it permits further elaboration in the symbolic processes.

This reviewer found the presentation quite interesting. However, it seems questionable whether the above hypotheses are proven. In many instances the patient seemed to free associate to the affect which was displaced onto the art productions, rather than to receive new insight from the form and content directly. While this was therapeutically advantageous, one wonders whether the same result could not have been achieved with classical analysis.

The idea of art as an adjunct in understanding preverbal conflict and therapeutic displacement of affect is stimulating and worthy of much more research. The book is recommended to dynamic psychotherapists.

H. F.

DER BLUTSPIEGEL. BY DR. MED. F. H. DOST, Professor an der Humboldt-Universität Komm. Direktor der Universitäts-Kinderklinik Charite, Berlin. Pp. 362; 96 ills. Leipzig: Georg Thieme, 1953. Price, DM 22.

THIS text deals with a large number of blood concentration curves of a variety of substances used in diagnostic and therapeutic medicine. It is a highly mathematical approach demanding some knowledge of calculus, logarithmic functions to the base "e", and so forth.

The absorption, concentration and disposition of various sulfonamides, crystalline and depot penicillins, monosaccharides, renal clearance substances, diphtheria antitoxin and antibodies are described along with many other substances, too numerous to mention.

W. S.

PSYCHOSIS AND CIVILIZATION. BY HERBERT GOLDHAMER AND ANDREW W. MARSHALL. Pp. 126. Glencoe, Ill.: The Free Press, 1953. Price, $4.00.

THIS book is an inquiry into the question of (1) whether there are any long term changes in the frequency of psychoses in the past 100 years; (2) whether it is possible to measure the risk of admission to a mental hospital in our society. The authors find that in the age group under 50 there has been no increase in psychoses in the past 100 years. They even question whether there has been any significant increase in the psychoses of old age. They discuss many factors which enter into expectancy of admission and conclude that this must remain largely conjectural. The statistics used and the discussion make constructive reading for the physician interested in the mentally ill.

O. E.

EXPERIMENTAL ATHEROSCLEROSIS. BY LOUIS N. KATZ, M.D., Director, and JEREMIAH STAMLER, M.D., Research Associate, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago. Pp. 375; 37 ills., 7 color plates. Springfield, Ill.: Charles C Thomas, 1953. Price, $10.50.

EVER since the publication of Anitschkow's work in 1913 there has been a progressively increasing volume of research into the relationship of lipid metabolism and atherosclerosis. As the years have gone by more and more investigators have come to accept the view that a definite relationship does exist, though the exact nature of the metabolic defect involved remains to be elucidated. As the amount of research has been increasing by geometric proportions there has developed a very real need for a volume summarizing the important extant knowledge. This has been admirably accomplished by Drs. Katz and Stamler who have done such a large amount of work on atherogenesis in the chick. Their

book should be of inestimable value to all who are doing work in this field, and it should be of great interest also to the internist and practitioner who desire a concise summary of the present status of knowledge of this important subject. A very valuable bibliography containing 713 references is included. The authors believe that "the recent emphasis on greater experimental endeavor and less comprehensive speculation" is a very healthy trend. T. D.

THE 1952 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY. Edited by HOWARD T. KARSNER, M.D., LL.D., and ARTHUR HAWLEY SANFORD, M.A., M.D. Pp. 400; 164 ills. Chicago: Year Book Publishers, 1953. Price, $5.50.

The present volume is comprised of abstracts of pertinent articles published from January through December, 1952. Its overall value and interest are enhanced by numerous editorial comments and selected illustrations. Pathologists and clinical pathologists will find this review useful in scanning progress in broad areas of laboratory medicine.
C. Z.

SCHÖPFERISCHE GESTALTUNG AUS DEM UNBEWUSSTEN. EIN ANALYTISCHES BILDERBUCH. BY M. SCHULTZE-NIEMANN. Pp. 45; 32 ills. Munich: J. H. Lehmanns Verlag, 1953. Price, DM 12.

THE presentation is that of the artistic graphic productions of a woman patient who, separated at an early age from her parents then living in tropical South America and taken to Germany where she was subsequently reunited with them. She, however, lost her beloved father when she was in the 29th year of her life. On account of a neurosis that developed she was subjected to psychoanalytic treatment. Very valuable in this treatment was the interpretation of her drawings, many colored with pastels. The interpretation was often, at least in part, that of the patient. The treatment lasted two years and was productive of about 300 pictures, 32 of which, arranged in order of production, are reproduced in this small volume, some of them in color. The treatment ended in apparent recovery.

The pictures are well reproduced and the explanation of their meaning is, on the whole, convincing. The variations of the mood of the patient are well reflected in them. She had had no formal training in art and she did not realize until after she had finished a picture just what it was that she had produced. To all appearances they arose in her unconscious.

The reproductions are good and the colors apparently excellent. The general impression produced by them before one reads the text is that they are, one may say, "semi-abstracts." An analysis of the productions of some of our painters of "abstracts" and a correlation of this with their known mental characteristics might produce an "arbeit" well worth while. M. M.

THE FOUNDERS OF NEUROLOGY. Edited by WEBB HAYMAKER, M.D., Chief, Neuropathology Section, Armed Forces Institute of Pathology, Washington, D. C. Pp. 435; 132 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $10.50.

"THE FOUNDERS OF NEUROLOGY" written by 84 present-day neurologists is a collection of 133 sketches of the lives of founders of Neurology, not, of course, complete. All of the neurological disciplines are represented.

The book is very good and is easy and fascinating reading, at least for any one with any interest in any aspect of neurology. The human failings and foibles which are not neglected only serve to increase one's appreciation of those pioneers who, working in the dark, exploring, bit by bit, made their observations and drew conclusions. This bit of specialty medical history once again points up the fact so often noted before that one had best be careful and search the literature diligently before laying claim to something as new.

The personal and oftentimes amusing details of some of the biographies, together with the fact that the book is such a magnificent memorial to those who have gone before, makes it almost a must for every physician.

If young men in medicine read it, the reviewer feels that its inspiration may well turn many to neurology as a life's work.
S. G.

A Translation of Luigi Galvani's DE VIRIBUS ELECTRICITATIS IN MOTU MUSCULARIS COMMENTARIUS. Commentary on the Effect of Electricity on Muscular Motion. BY ROBERT MONTRAVILLE GREEN, M.D., Emer. Prof. of Anatomy, Harvard Med. School. Pp. 97; 4 tables and portrait. Cambridge: Elizabeth Licht, 1953. Price, $4.00.

THIS pioneer work on electrophysiology, one of Galvani's masterpieces, has held the interest of the scientific world for more than 150 years. Fulton and Cushing published as late as 1936 (Annals of Science, **1**, 239) a rather lengthy bibliography of the writings of Galvani and his nephew, Aldini, on the subject of animal electricity; yet this work on the effect of electricity on muscular contraction has apparently never before been translated into English. First published, in Latin, of course, in the Commentaries of the Bologna Institute and Academy of Arts and Sciences in 1791 (vol. 7, pp. 363-418), it was issued the next year in book form together with a Dissertation on the Origin and Development of the Theory of Animal Electricity by Aldini. Both of these are included in the present book together with an exchange of letters between Carminati and Galvani, translated from the Italian. Though G. C. Pupilli speaks in the Introduction of the literary excellence of Galvani's writings, to the Reviewer the text is frequently obscure, prolix and redundant, even allowing for the turgid style of that period and the necessarily scanty vocabulary of the infant science. This is especially prominent in the final section on conjectures and conclusions.

Of the 4 parts of Galvani's Commentary, the first two deal with the "artificial" variety where the muscle action is produced by extraneous electricity transmitted through animal tissues. In part 3, on "innate" or inherent animal electricity, the muscle contractions were described as produced by connecting nerve and muscle by certain "electrophores". By 1794, Galvani, stimulated by certain objections of Volta, elicited the polarization potential of muscle by producing a contraction when the cut end of a frog's nerve was applied to a muscle. This and the demonstration of "injury potential" in nerves (1797) are claimed by Pupilli to mark the beginning of electro-physiology. Too bad that these could not also be included in the present book, to complete the story of Galvani's contribution to this field of such importance to both electricity and physiology. E. K.

MECHANISMS OF UROLOGIC DISEASE. By DAVID M. DAVIS, M.D., Professor of Urology, Emeritus, Jefferson Medical College, Philadelphia. Pp. 156. Philadelphia: W. B. Saunders Co., 1953. Price, $4.50.

DR. DAVIS has approached the main problems in urology from the standpoint of their pathology and physiology. He has attempted to give to the average practitioner a simple and concise background for the management of urologic diseases. In the majority of chapters of his book he has succeeded.

Of particular excellence are the chapters on Neurogenic Changes, Stone Formation, Obstruction, and Infection. There is a very good section entitled "Catheterization", which should be read by every intern and resident, in that it provides a very valuable guide for the young doctor who is being exposed for the first time to the essentials of management of surgical patients.

This book had its origin in lectures to medical students, and its value to them and the young physician is inestimable. For the older physician and urologist, it provides a simple and refreshing approach to the complicated problems of urology. T. H.

VENEREAL INFECTIONS AND TREPONEMATOSES. Fourth Report of the WHO Expert Committee on Venereal Infections and Treponematoses. Pp. 84; 19 ills. Geneva: World Health Organization, 1953. Price, $.55.

THIS report, which has recently been published as No. 63 in the World Health Organization: Technical Report Series, is, in effect, a summary record of present knowledge concerning the control of treponemal diseases. It is particularly important as a source of information on the conduct of mass campaigns against non-venereal treponematoses: yaws, bejel, pinta, "njovera", and endemic syphilis. Considerable experience in carrying out such campaigns has been gained in recent years, when many governments have undertaken large-scale control programs with the aid of international organizations such as UNICEF and WHO.

The committee's report covers all the phases of mass treponematoses: control programs, drugs and therapy, and serodiagnosis and other laboratory aspects; in addition, it deals briefly with personnel training for venereal-disease-control work, the control of venereal disease among seafarers, and non-treponemal venereal infections. J. K.

DAS OBERE KREUZ. PSYCHOTHERAPIE BEI ERKRANKUNGEN DER HALSREGION. By DR. HELMUTH STOLZE. Pp. 151; 8 ills. Munich: J. F. Lehmanns Verlag, 1953. Price, DM 14.

THE author has traced, in many of the cases of symptoms affecting the cervical region in the cases he was dealing with, a psychosomatic or a neurotic factor. Of 285

cases in which the cervical region of the spine or the neck region was involved, in 55.5% he was dealing with, from an organic standpoint, a cervical vertebral syndrome, perhaps associated with trouble with the intervertebral discs; in 28.0% of cases there were signs of tetany; and in 16.5% of cases a combination of these. (It is the impression of the reviewer that tetany or a latent tetany is not so common in the U.S.A.). Of the cases over 40 years of age, 109 of 139 showed cervical syndrome. Of the 190 cases in which there was no demonstrable lesion of the cervical spine, 63 showed the cervical syndrome, 80 latent tetany, and the rest a combination of the two. Of the 190 cases, 130 showed mental or neurotic symptoms.

The author considers the neck as an "organ", this region being regarded as a condensed functional unit through which various systems pass (the supporting apparatus, the apparatus for movement, part of the peripheral nervous system, also part of the vegetative nervous system, part of the respiratory system and of the digestive system, some of the endocrine system). The author reports 19 cases more or less *in extenso*, and has dealt with the psychical aspects of these cases, in some of whom he used dream analysis and interpretation, calling attention to various conflicts that were associated with the disturbances, and the resolution of these conflicts, sometimes under hypnosis. Among the other methods employed by him were extension, postural exercises and massage, full baths, ultraviolet treatment, and short waves. "Autogenous training" was utilized in some of the cases, as well as social therapy and group therapy. M. M.

HENRY VIII. A DIFFICULT PATIENT. By SIR ARTHUR SALISBURY MACNALTY, K.C.B., M.D., F.R.C.P., F.R.C.S. Pp. 202; portrait frontispiece. Medical Viewpoint Series. London: Christopher Johnson, 1952. Price, $4.00.

THIS character study, by an eminent medical historian and public health authority, gives a clear and interesting picture of one of England's most photogenic sovereigns. A much wider scope is covered than the title suggests, medical details being given but little more prominence than the political or theological. The book, however, should give pleasure and profitable instruction in all the aspects treated. Henry's medical "case record" is summarized in a brief Appendix, which finds no reliable evidence in favor of the tuberculosis that was rife in his family, or syphilis or gout, as would be suggested by his life-long indulgence in high living. Following the line of Froude's History (1856) and Frederick Chamberlin's sympathetic "Private Character of Henry the 8th", MacNalty has avowedly given his difficult patient the benefit of his praiseworthy early career in interpreting his later actions. Henry's first 35 years: the healthy, patient, handsome, "bluff King Hal": are sharply contrasted with the ailing, capricious tyrant of his last 11 years. The author takes a serious head injury that the King suffered while jousting as the turning point in his behavioral pattern, and a chronic "sorre leg" (leg ulcer, probably of varicose origin) as the start of and the background for his physical decline. MacNalty pictures Henry as courageous and ever attentive to his country's needs, even when failing health should have greatly restricted his activities, and even regards him as the most learned, accomplished and forceful King of England. He attributes Henry's death, at the age of 55, either to a cardiac or pulmonary complication of his chronic ulcer or to uremia, a differential diagnosis that without a necropsy may not be possible even today. E. K.

THE WORK OF WHO, 1952. ANNUAL REPORT OF THE DIRECTOR-GENERAL TO THE WORLD HEALTH ASSEMBLY AND TO THE UNITED NATIONS. Pp. 204; 17 pages of ills. Geneva: World Health Organization, 1953. Price, $1.25.

THE need for maintaining a sound balance between the health programs of a developing country and its general economic and social progress is emphasized by Dr. Brock Chisholm, Director-General of the World Health Organization, in the Introduction to his Annual Report for 1952.

The assistance of the Organization has been given mainly to the countries which are, economically, the least developed. The Director-General emphasizes, however, that owing to such countries' lack of capital, their possibilities of effecting lasting improvements through the help of international organizations are severely limited.

The Report, covering the fourth full year of work of the Organization describes what has been attempted and achieved by WHO in directing and co-ordinating international health work.

Commenting upon current trends, the Director-General points out how the growing

interest in the preventive and social aspects of medicine is being reflected in the attitude of doctors and in the type of training given to medical students. J. K.

EXPERIMENTAL STUDIES IN PSYCHIATRIC ART. BY E. CUNNINGHAM DAX, B. SC., M.B., B.S., D.P.M., Chairman Mental Hygiene Authority, Victoria, Australia. Pp. 100; 51 ills. Philadelphia: J. B. Lippincott Co., 1953. Price, $5.00.

THE book presents data in an attempt to answer the following questions: (a) Are the reflections of mental illness in the paintings of patients an aid to diagnosis? (b) Has painting any therapeutic value as used in the mental disorders and in the psychoses in particular? (c) Do the same effects apply to music as to painting? (d) Is the expression of music in terms of painting a useful means of investigating its effects? (e) Are these methods of assistance in the investigation of the characteristics of head injury? (f) Do the results of these experiments further the study of the reciprocal relationship between art and illness? The authors feel that the answers to these questions are generally positive.

In the presentation following the general discussions of creative activity, organization of painting and examination of patients' pictures, there is a discussion of the symbolic meanings of the eye, musical investigations, the use of synesthesia for musical recordings, painting and cerebral injury, the relationship of art and illness, and the conclusions.

The book is an interesting and worthwhile contribution in this field and is recommended to all interested in these subjects and psychotherapy. H. F.

ASPECTS OF THE PSYCHOLOGY OF THE TUBERCULOUS. BY GORDON F. DERNER, PH.D. Pp. 119. New York: Paul B. Hoeber, 1953. Price, $3.50.

THIS book is a study of 32 patients in the Tuberculosis Division of Grasslands Hospital, Valhalla, New York. They were first admissions between 2 months and 2 years. Average age 25.4 and averaging 13.3 years of education.

Psychological tests as well as clinical interviews were carried out.

Some of the findings were as follows:

"There was no unique tuberculous personality demonstrated in this study but there was a wide variety of disturbed behavior.

"The Rorschach Test, as usually clinically interpreted, indicated low productivity. There was low affectivity, emotional impoverishment, and impoverished intellectual productivity. There was introversion and some emphasis on body-oriented ideas.

"The most frequent emotions were fear, apprehension, and depression. Most patients were optimistic about their prognosis but they did not show *spes phthisica*. All patients had some degree of depression related to the disease from time to time during the course of the disease.

"The most frequent changes in the sanatorium suggested were better food, more individual medical interpretation, and other patient services such as better nursing and psychological services."

A few conclusions were:

"The diagnosis and treatment of tuberculosis necessitates a consideration of the patient's fears and concerns related to the disease and its concomitants. The approach to the patient should be psychotherapeutic in orientation.

"Because tuberculous patients tend to view their handicap realistically they will accept realistic life goals. Rehabilitation procedures coupled with psychotherapy may help the patient choose a life goal appropriate for him.

"The effectiveness of psychotherapy as an adjunct to the present prescribed methods of tuberculosis treatment offers an important research problem." O. E.

GYNÄKOLOGISCHE ORGANNEUROSEN. BY PROF. DR. HANS ROEMER, Director of the Women's Clinic of the Medical Academy, Giessen. Pp. 190. Stuttgart: Georg Thieme Verlag, 1953 (Grune & Stratton, New York, U. S. Agents). Price, DM 13.50.

THIS publication is an excellent review of the so-called organ neuroses of the female with special reference to the genital organs. It is written primarily for the gynecologist and for the practitioner who deals with gynecological disorders. The nature of the psychosomatic disorders of the female is fully explained and analyzed. This does not mean that each case (and there are many reported *in extenso* here) has been psychoanalyzed, since in many of them psychoanalysis was not necessary, some of them recovering soon after the beginning of treatment directed to the unveiling of the initial psycho-experiential trauma that gave rise to the conflict. However, the symptomatology

presented by each patient was such as to lead to the suspicion that a conflict was present.

The means of treatment: suggestion, association tests, analysis and interpretation of dreams, and general, especially psychotherapy, are entered into thoroughly, after a preliminary dissertation as to how symptoms of this nature come to be formed, and chapters on pathogenesis and diagnosis.

We believe that the brochure will serve an excellent purpose in orientating the gynecologist to the advantages of the psychosomatic approach to the cases he deals with. M. M.

TWENTY YEARS OF PSYCHOANALYSIS. Edited by FRANZ ALEXANDER, M.D., and HELEN ROSS. Pp. 309. New York: W. W. Norton & Co., 1953. Price, $3.75.

THIS is a book dealing with the progress of psychoanalysis in the United States during the past 20 years. The senior editor, Dr. Alexander, is well qualified to bring this book forth since he is one of the foremost of the psychoanalysts interested in the integration of psychoanalysis as a discipline among both medical and the social sciences. He has obtained able people to discuss such subjects as Psychoanalysis in Medicine and Psychoanalysis in Psychiatry.

Part two of the book is devoted to Training and Research at the Chicago Institute for Psychoanalysis: the institution where Dr. Alexander has exerted such a wide and fruitful influence as Director. The book makes valuable and interesting reading for the physician who is interested in the role of dynamic psychology in medicine and the social sciences. O. E.

YOUR FEET ARE KILLING YOU. BY SIMON J. WIKLER, Doctor of Surgical Chiropody. Pp. 214; 8 ills. New York: Frederick Fell, Inc., 1953. Price, $3.50.

A few years ago, surgeons put down their scalpels and replaced them with pens. The result was an almost flooding of our book market with quasi medical texts. With time, this phase of American literature gradually passed. It would now seem that we may have chiropodists lay down the tools and take pen in hand. If such is the case, Dr. Wikler can be considered the lead off man. This, his initial text, has very little to offer. Its only contribution is to remind the public that most foot ailments, in the basically normal foot, are the result of shoes that are of incorrect fit and design. However, there is no illustration of a type shoe one should seek among the many on today's market.

The illustrations in the text are fair, but entirely too meager. Most of us are aware that foot disability and disease can be a distinct problem. However, it is my opinion that the author is stretching things too far when he hypothesizes that foot disease may be a causative factor in certain carcinomas, rheumatic fever, diseases of the uterus, sexual disturbances, essential hypertension, chronic alcoholics, and even brain tumors.

The section on treatment can be considered satisfactory, and certainly indicates the author has had considerable and varied management of the foot.

In conclusion, the text was a disappointment to this reviewer. Such being the case, I would prefer not to recommend it to the laity, medical students, nurses, or physicians. A. S.

HEREDITY IN HEALTH AND MENTAL DISORDER. BY FRANZ JOSEF KALLMANN, M.D. Pp. 315; 89 ills. New York: W. W. Norton & Co., 1953. Price, $6.00.

THIS book is a further contribution to the problem of heredity particularly in mental disease. To read this book is to realize that there is still quite a wide gap between the interpretation of what the author calls the "genetically trained psychiatrist" and the psychodynamically trained psychiatrist. For example, after discussing certain differences between two-egg twins and one-egg twins and finding some traits more common in one-egg twins he says "Since these differences in normal twin pairs cannot plausibly be explained on grounds of measurable variations in environmental influences, it is justifiable to classify them as genetically determined." To the reviewer such a conclusion leaves out of consideration the factor of seeing a mirror image of oneself all the time as opposed to a different gestalt. It leaves out of consideration the reactions of others in the environment to the varying appearances of the children (and these reactions may vary greatly).

Twins are presented who are concordant as to mental disease and some who are discordant. An interesting figure occurs in relation to suicide. Of 18 one-egg twins and 21 two-egg twins all remained discordant except one pair and the author concludes that, "in short, suicide is one of the few phenomena unlikely to occur in both twins even under suicide conditions of maladjustment and pri-

vation." In discussing schizophrenia, the author says "Detailed fertility studies, however, show that the total reproduction of schizophrenics is much lower than that of a comparable general population, especially in the deteriorating types of schizophrenia. Since a person with severe symptoms is less likely to produce children, a schizophrenic who has children is apt to have relatively mild symptoms and therefore a comparatively high degree of resistance to the disease. The factors producing this resistance will be passed on to the children. Where both parents are schizophrenic, the children will inherit this capacity for resistance from both parents." To a psychodynamically orientated psychiatrist there is "infection" not resistance developed when children are exposed to schizophrenic parents.

In neurological disease, including epilepsy much more concordance is found in one-egg twins. But with the many variables which environment offers it seems premature to draw dogmatic conclusions concerning genetics and mental disease.

A section of the book is devoted to genetics in mental health planning. Suggestions for a counseling agency on genetics in the community are brought forward. An excellent bibliography is included.

A few years ago there was a book written by a clergyman and a psychoanalyst in which each gave his interpretation of the same phenomena. It would seem that this idea could profitably be carried out in a joint study by the genetically trained psychiatrist and the psychodynamically trained psychiatrist. Then the medical profession would have a better opportunity to weigh both sides of a very important problem. O. E.

ATLAS OF REGIONAL DERMATOLOGY. By ERNEST K. STRATTON, P.D., M.D., Research Assoc., The George Williams Hooper Foundation for Medical Research, University of California Medical Center. Pp. 274; 603 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $15.00.

THIS is the second book dealing with regional dermatology which has appeared in recent years from the San Francisco area. This volume "is intended primarily for the student who needs visual help in identifying skin diseases", and consists of an outline of dermatology in atlas form which presents regional groupings of most of the common cutaneous disorders. In a general way the clinical illustrations, with some exceptions, are good; the color reproductions by Fasal, first class; but those dealing with histopathology are on the whole of doubtful value. The sections on the acute infectious diseases and leprosy have been prepared by acknowledged authorities (Costello, Koplik, and Arnold).

Unfortunately, the regional method of presentation leads to numerous duplications with varying suggestions for therapy of the same disease. Furthermore, the student will, on occasion, have difficulty in determining the correct terminology of a disease since the same process is titled variously on different pages. To illustrate with one example: On page 48, dermatosis papulosa nigra is "dermatitis" papulosa nigra, but on page 51, (Fig. 100) it is correctly called "dermatosis" papulosa nigra. The index on page 268 has it "Dermatitis papulosa nigra, of face, 51 (Fig. 100)." "Dermatosis papulosa nigra" is not indexed.

Regional presentation of the superficial manifestations of dermatology seems to be a "natural" but to the uninitiated in adequate explanation, will tend further to solidify the view that dermatology is in fact a superficial specialty. In spite of being practical, regional presentation needs to be supplemented somewhere in the text by a clear statement of the internal medical implications of diseases of the skin. If this basic fact is well understood, Stratton's book will serve as a useful guide for the student who sees a patient with the presenting lesions in a particular anatomical region. H. B.

BALLISTOCARDIOGRAPHY. By WILLIAM DOCK, M.D., State University Medical Center at New York, HARRY MANDELBAUM, M.D., State University Medical Center at New York, and ROBERT A. MANDELBAUM, M.D., Jewish Hospital of Brooklyn. Pp. 293; 139 ills. St. Louis: C. V. Mosby Co., 1953. Price, $9.50.

THE science of ballistocardiography though still in its infancy, has been making progress through studies of patients and from experiments on human cadavers. The present status of this subject, including a description of the various instruments commonly used, the techniques involved, the physiologic basis of the deflections, and the patterns associated with normality and various disease states is the subject of this volume. It is intended for those who are beginning to explore this field, and the clarity of the presentation is so excellent as to make it very commend-

able for this purpose. The chapter on Reading and Classifying handles very well the problem of the "normal" patient with an abnormal tracing and the danger of iatrogenic heart disease. There is an excellent bibliography which includes 259 references. This book is to be recommended to all those beginning the study of this subject, both those who are using the technique and those who desire a better understanding of the reports of consultants. T. D.

PATHOLOGY OF THE CELL. By G. R. CAMERON, M.B., D. Sc. (MELB.), Director of the Graham Research Laboratories and Prof. of Morbid Anat., University College Hospital Medical School, University of London. Pp. 840; 105 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $22.50.

THIS is a scholarly treatise on the pathology of the cell. The volume is divided into 4 major parts: I. The Normal Cell, II. The Abnormal Cell, III. Critical Discussion of the Cell Theory, and IV. The Cellular Pathology of the Future. In addition, there is an extensive bibliography, 126 pages in length.

As can be appreciated, the author undertook a monumental task to which he devoted 11 years of continuous work. The result is a readable and valuable reference volume, which will be useful to research workers in the basic sciences, especially pathologists and physiologists. C. Z.

TEXTBOOK OF GYNECOLOGY. By JOHN I. BREWER, M.D., PH.D., Prof. Obstetrics and Gynecology, Northwestern University Medical School. Pp. 532; 146 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $10.00.

IN the interesting Textbook of Gynecology, which is prepared especially for the student attempting to master the fundamentals of the subject, the author attempts to present the material in a manner similar to that in which it will be utilized in the study of patients.

In Part I, gynecologic disorders and diseases are presented in the conventional manner. The abnormalities affecting each portion of the genital tract are discussed separately in terms of etiology, diagnosis and management. For the more important lesions the accompanying pathologic changes also are discussed and illustrated.

Part II is devoted to a consideration of (Bearing-down Discomfort, Leukorrhea, Dysmenorrhea, Abnormal Uterine Bleeding, Bleeding and Pain, and so forth) and subjects such as Sterility and Amenorrhea. At the beginning of each section the conditions which could produce the symptom are listed, and in the text each is discussed in detail and differential diagnostic methods are completely and specifically outlined and means of treatment are suggested.

The text is illustrated with many photographs which are clearly reproduced; the photomicrographs are clear and in most of them the details of the pathologic change can be made out.

The author believes that by eliminating unnecessary details and unsubstantiated theories and by presenting the material as it must be utilized in the study of a patient with a gynecologic complaint the student will obtain a more practical understanding of pelvic disease. This book certainly should prove valuable in hastening the conversion of isolated bits of partially correlated information to usable knowledge. It should be helpful not only for the medical student but also for residents and general practitioners. J. W.

CLINICAL MANAGEMENT OF BEHAVIOR DISORDERS IN CHILDREN. By HARRY BAKWIN, M.D., and RUTH MORRIS BAKWIN, M.D. Pp. 495; 14 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $10.00.

THIS book is fairly comprehensive on the subject of behavior problems in children. It begins with growth and development patterns and then takes up the psychological care of the physically ill and handicapped. It then has a chapter on diagnosis and treatment, and goes on to such phenomena as intellectual function and developmental abnormalities in speech, writing, spelling, enuresis, and others.

The latter part of the book deals with personality trait disturbances such as anger, aggression, negativism, and sexuality. Problems of habit training such as eating, tics and sleep are also discussed. A chapter is given to organic disturbances with a large psychic component such as asthma, skin conditions and colitis. Antisocial behavior is dealt with and a special section is devoted to topics such as accident proneness and schizophrenic reactions. The book is written in a clear, easily understood style. The approach to problems is entirely modern and the book is recommended for doctors, teachers and parents; in short all who work with children. There is both an author and subject index. O. E.

NUTRITIONAL STUDIES IN ADOLESCENT GIRLS AND THEIR RELATION TO TUBERCULOSIS. By JOSEPH A. JOHNSTON, M.D., Pediatrician-in-Chief, Henry Ford Hospital. Pp. 320; 106 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $7.50.

THE influence of the nutritional status upon tuberculous infection in adolescent girls has been extensively studied by means of long-term balance determinations of nitrogen and calcium. Correlations between metabolic observations and the clinical status of the patient including Roentgen-ray findings are presented in considerable detail. These data indicate that a favorable course of the infection was accompanied by an adequate nitrogen storage. Lesser degrees of nitrogen retention or nitrogen losses were associated with spread of the disease. While the level of calcium balance bore no constant relationship to activity of tuberculosis, some interesting observations are recorded. The influence of various hormones and other factors upon metabolic balances is summarized from the author's experience. This monograph may well serve as a model for similar contributions relating to other disease states. C. S.

THE OBSTETRICAL FORCEPS. By L. V. DILL, M.D., F.A.C.S., Head, Obstetrics and Gynecology, Yater Clinic; Asst. Prof. Obstetrics and Gynecology, Georgetown University School of Medicine. Pp. 156; 86 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $5.25.

THE need for a monograph on obstetric forceps is indicated by the fact that no complete work on the development and use of the instrument has been published in English. The author has admirably corrected this defect in this book. The origin and development of the instrument is traced in an interesting and informative manner and the most often used modern types are described and illustrated. The indications for forceps delivery and the manner in which it is carried out with the commonly used instruments are clearly presented. The 86 illustrations, most of which are pen and ink drawings depicting the techniques for application of the blades and for delivery, are well reproduced, well placed and illustrate the text well. Although no new concepts are presented this book does concentrate a good bit of valuable information concerning the obstetric forceps and should be of great help to the obstetric resident, the general practitioner and, as well, the practicing obstetrician. J. W.

RUDOLF VIRCHOW: DOCTOR, STATESMAN, ANTHROPOLOGIST. By ERWIN H. ACKERKNECHT. Pp. 304; 3 ills. Madison: U. of Wisconsin Press, 1953. Price, $5.00.

MOST any properly educated physician would willingly maintain that Virchow was one of the really great figures in modern medicine but few indeed could support such a view with concrete evidence. His celebrated book, *Cellularpathologie* (1858), no more created a new line of endeavor than did Schwann's discovery create the Cell Theory, though both are entitled to major credit; if credit evaluation is desirable in considering scientific progress; for having added considerably to and firmly established the new concepts.

This book is full of surprises: the first coming in the Preface with the remark that "this is the first full-length study of Virchow in any language" and that it should appear in English, not in German. It is not surprising, in view of Virchow's eminence in three or four different fields (Medicine and Public Health, Politics, Anthropology) that in 304 pages not a few important topics are passed over very briefly. However, we should be grateful for what we have; perhaps the author's remarks about Virchow's extensive personal archives, now in Soviet-Germany, provide a hint that a larger, more complete study may later be attempted. Especially should this include more about Virchow's family life and his ability to teach, and a much more detailed index. The present work starts with a synthetic life history that, while necessarily overlapped by occasional later chapters, gives a lively portrait of this energetic, fearless, gifted, highly critical character who was often wrong, but more often right. The author, obviously an enthusiastic admirer of one of the great men of the 19th century, has maintained an objective attitude that unsparingly reports his hero's contentiousness and obstinacy, his inconsistencies and tendency to boastfulness.

In the chapter on the Doctor, the longest and one of most interest here, Virchow's personal achievements in pathology are considered, to be sure, but more emphasis placed on his tendency to work through institutions, and the influence of the two great periodicals that he founded and edited. His pathological discoveries, about which we learned as students; amyloid, hematoidin, leukemia and the rest; are comparatively neglected here in favor of more general matters. Discussions of his concepts of pathology, of the significance of his concern with physiology and clinical medicine, as in the

title of his great Archiv and his early work in physiological and chemical pathology are instances that come to mind. One of his most important studies, on thrombosis and embolism, was as much physiology as morbid anatomy, and in fact, as Ackerknecht observes, his *Gesammelte Abhandlungen* (1856) could very well have been called an essay in pathological physiology. He also points out that Virchow's most noted achievement: the establishment of cellular pathology (1858) and the motto, *omnis cellula e cellula* (Raspail, 1825): were original with him only in the sense that they established concepts earlier described by Schwann and various predecessors. *Cellular Pathology*, however, seems to Ackerknecht worth a short paragraph for each of its 20 (later 22) chapters and to the Reviewer is less obsolete today than the uncompleted 3 volume *Krankhafte Geschwuelste* (1863). Adverse criticism, however, should be especially sparing here. For example, as Virchow himself recognized that "Tumors" was a classification dictated by practical needs, the inclusion of tumors by extravasation (such as hematoma) and by granulation (such as syphilis) is defensible without quibbling.

In a short 13 pages, the author gives a sympathetic picture of Virchow's attitude toward bacteriological discoveries: usefully critical, rather than unqualifiedly opposed. We must agree with him, too, that the cell, the only source of other cells, still is an ultimate biologic unit. He praises highly Virchow's contributions to Medical Reform and to Public Health which reached into almost every phase of German life and "preserved more lives in the past century than all our . . . individual therapeutics combined."

The sections on the Statesman and the Anthropologist, short as they are, give a fair idea of Virchow's important contributions to these fields. Medical men will be surprised to learn how big a role politics played in Virchow's life, but should expect, and find here, that he was always on the side of the working man, manning the barricades in '48, even at times joining with his arch enemy, Bismarck, who had once challenged him to a duel, and serving many years in the Prussian Diet and the Reichstag. However, even Ackerknecht's training in modern history and his skill as a biographer fail to bring life into the dull and necessarily unpermanent achievements of this side of Virchow's career. German anthropology, which he cultivated productively through most of his professional life, owed much to his efforts. As founder of the Berlin and German Societies and regular attendant at International Congresses for 30 years, Editor of three special journals, procurer of collections and the money for expeditions and so on, he held a position in anthropology, according to the author, that was eventually more authoritative than his position in medicine. His personal achievements were far less, though his early work in Pomerania and with Schliemann in the Near East are still remembered.

If Virchow had to wait a full half century for a true biography he is fortunate in having it written by one, who, born and brought up in Virchow's home province, took degrees in both medicine and anthropology. The book is both a worthy addition to the record of the great period of German medicine and one that carries many useful lessons for the future.

E. K.

THE ALKALOIDS, VOLUME III. Edited by R. H. F. MANSKE AND H. L. HOLMES, Dominion Research Laboratory, Guelph, Ontario, and the Carwin Company, North Haven, Connecticut, respectively. Pp. 422. New York: Academic Press, Inc., 1953. Price, $11.00.

THIS is the third of a series of five volumes which have been planned to review the chemistry and pharmacology of the alkaloids. Like the first two volumes, it has been prepared by an international group of experts, some chapters representing the collaborative work of two authors.

The present volume covers the following groups of alkaloids: Cinchona, Quinoline other than those of Cinchona, Quinazoline, Lupin, Imidazole, Solanum and Veratrum, β-phenethylamines, Ephedra, and Ipecac. The discussions are presented in the same thorough, well-documented but interesting fashion which has characterized Volumes I and II. The explanations of chemical relationships are particularly well presented and illustrated when one considers the complexity of the structures which are involved. While it is the obvious intent of the authors to offer primarily a chemical treatise, the text includes numerous references to pharmacological studies.

J. S.

NEW BOOKS

Tests and Standards for New and Nonofficial Remedies. THE CHEMICAL LABORATORY, AMERICAN MEDICAL ASSOCIATION. Pp. 327. Philadelphia: J. B. Lippincott Co., 1953. Price, $4.00.

THIS book describes the tests for identity, quality and purity of drugs and dosage forms which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1, 1953. Formerly these

analytical methods were published in one volume with New and Nonofficial Remedies, which describes the actions and therapeutic uses of these drugs. Since these laboratory tests are of little use to physicians using New and Nonofficial Remedies, the tests have been separated into a volume which is essential for the pharmacist and the chemist in the pharmaceutical industry. As a result both books are of convenient size. G. F.

The Role of Growth Hormone in Carbohydrate Metabolism. By R. C. DeBodo and M. W. Sinkoff, Dept. of Pharmacology, New York Univ. College of Medicine. Taken from Ann. New York Acad. Sci., **57**, 23, 1953. Pp. 37; 14 ills. New York: New York Academy of Sciences, 1953. Price, $1.00.

This is an extremely interesting monograph on the growth hormone which concerns the relationship of this hormone to carbohydrate metabolism. W. P.

The British Encyclopaedia of Medical Practice, Medical Progress, 1953. Edited by The Lord Horder, G.C.V.O., M.D., F.R.C.P. Pp. 384; 15 ills. London: Butterworth & Co., 1953. Price, not given.

The Year Book of General Surgery, 1953-1954. Edited by Evarts A. Graham, M.D. Pp. 590; 150 ills. Chicago: Year Book Publishers, 1953. Price, $6.00.

Mechanism of Corticosteroid Action in Disease Processes. By Gregory Pincus and Oscar Hechter, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass. Taken from Ann. New York Acad. Sci., **56**, 625, 1953. Pp. 192; 57 ills. New York: New York Academy of Sciences, 1953. Price, $3.50.

This collection of papers will be extremely valuable to physicians interested in the action of Cortisone. Many of the presentations are of fundamental value. W. P.

Josiah Macy, Jr. Foundation, 1950. Twentieth Anniversary Review. Pp. 111. New York: Josiah Macy, Jr. Foundation, 1953.

Plant Proteins in Child Feeding. Medical Research Council Special Report Series No. 279. By R. F. A. Dean. Pp. 163. London: Her Majesty's Stationery Office, 1953. Price, $2.25.

The monograph details feeding experiments (field studies) to evaluate the adequacy of plant proteins as substitutes for protein of animal sources. Though the value of such information in this country is limited largely to its relation to therapeutic diets (allergy), it has far reaching importance as a means of attacking the problem of undernutrition in many countries throughout the world. The data has to do with the use of cereal and soy bean mixture as a complete and partial milk substitute. The data are of value for those working in the field of nutrition W. N.

Ophthalmologic Diagnosis. By F. Herbert Haessler, M.D. Pp. 387; 151 ills. Baltimore: Williams & Wilkins Company, 1953. Price, $8.00.

The value of this manual lies entirely in the personal experiences of the author, which are scattered throughout the book. It is not a useful text, and could hardly be of interest to either medical students or general physicians. The illustrations are woefully inadequate. F. A.

Physiological Methods in Clinical Practice. By William S. Middleton, M.D., Department of Medicine, University of Wisconsin. Pp. 40. Springfield, Ill.: Charles C Thomas, 1953. Price, $1.00.

All physicians can read Doctor Middleton's splendid lecture with interest and profit. Its title clearly and concisely defines its message. R. K.

Growth of Protozoa. Annals New York Academy of Science, Vol. 56, Art. 5, pp. 815-1094. Edited by S. H. Hutner and William Trager, Conference Chairmen. Pp. 279; 69 ills. New York: New York Academy of Science, 1953. Price, $4.50.

A series of interesting articles on growth requirements of protozoa and on artificial culture of various protozoa pathogenic to man. R. K.

Second Report. Joint ILO/WHO Committee on Occupational Health. World Health Organization Technical Report Series, No. 66. Pp. 30. Geneva: World Health Organization, 1953. Price, $.20.

The Green and Red Planet. By Hubertus Strughold, Department of Space Medicine, U. S. Air Force School of Aviation Medicine. Pp. 103; 13 ills. Albuquerque, New Mexico: Univ. of New Mexico Press. 1953. Price, $4.00.

An interesting treatment of the possibility of vegetation and animal life on Mars is contained in this book. It deals with a new and unexplored field of biology, that of planetary ecology. This is the science of planets as an environment for life. It can be read with profit. M. O.

Chemical Physiology of Contraction in Body and Heart Muscle. By A. Szent-Györgyi, Institute of Muscle Research at the Marine Biological Laboratory, Woods Hole, Massachusetts. Pp. 135; 29 ills. New York: Academic Press, Inc., 1953. Price, $4.80.

This is an outstanding work by an authority in the field. Workers in this specialty will find it very useful. The book is logically divided into the molecular mechanism of motion, a study on heart muscle fiber and finally interpretations. While the whole book is valuable, the parts on staircase (treppe), digitalis and on other drugs are very pertinent for medical men. M. O.